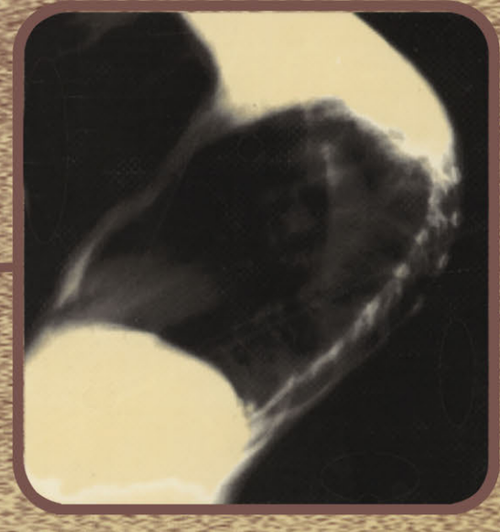
# *Atlas of* OSTEOPOROSIS

**Eric S. Orwoll**
*Editor*

**Stanley G. Korenman**
*Series Editor*



**SECOND EDITION**

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# OSTEOPOROSIS
## Second Edition

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# Preface

Osteoporosis has long been known to be a major health care problem, in both individual and public health terms, but in the last two decades tremendous increases in scientific inquiry have yielded a much greater understanding of the basic biology, clinical character, and epidemiology of this condition. These advances have been translated into much more sophisticated and effective tools for clinicians to use in the prevention and treatment of the disease. These tools, initially available only to specialists in endocrinology and rheumatology, are now taken advantage of by a wide range of disciplines, and their application is being adapted to a large variety of situations. Appropriately, the public is also becoming more educated about these issues, and it is not uncommon for clinicians to have sophisticated discussions with well-read patients about the diagnosis, prevention, and treatment of osteoporosis.

In this light, the Second Edition of the *Atlas of Osteoporosis* is designed to be useful to a broad readership united in their interest in the disorder. The expert authors have encapsulated not only the well-established basics of osteoporosis but also new developments in the field in a format that makes extensive use of graphical displays of important data.

Issues that are well known to be important to skeletal biology and osteoporosis (*eg*, nutrition, exercise, and growth) have been updated. That there is substantive new information in these areas is a testament to the vigor of the field and the pace of its advancement. Some chapters included in the First Edition have been more extensively revised to reflect major developments. For instance, the renewed realization of the importance of bone biomechanics has led to tremendous research activity in this area. Similarly, the idea that anabolic therapies might allow new bone to be added has been realized with the recent demonstration of the effectiveness of parathyroid hormone treatment for osteoporosis. Finally, several chapters have been added to highlight the emergence of new fields (genetics) or the expansion of others (bone densitometry and the laboratory evaluation of bone disorders). The editor and authors endeavored in this latest edition of the *Atlas* to preserve the considerable strengths of the First Edition and at the same time improve on it through the addition of new information.

Although osteoporosis has been recognized for millennia, the knowledge regarding this disorder continues to evolve. The sheer volume of available information, as well as its complexity, poses considerable challenges to those attempting to summarize it. To whatever extent the *Atlas* has succeeded in this endeavor, it is a tribute to the expert authors who devoted time and considerable expertise to the effort. Their contributions should enable the reader to comprehend the current state of this art, and to benefit from it.

**Eric S. Orwoll, MD**

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# Contents

# 1

# THE NATURE OF OSTEOPOROSIS

*Eric S. Orwoll and Robert Marcus*

The recent emergence of osteoporosis as a major focus of investigation in fields as diverse as mechanical engineering, pediatrics, and epidemiology has led to many important advances in the understanding of and therapeutics for this disease. Whereas the topic of osteoporosis formerly occupied just a few paragraphs in standard texts, it is now the primary focus of several journals and textbooks. This volume provides current information regarding skeletal health and its disruption. Attention is given to bone acquisition during growth years, mechanisms of adult bone loss, and new developments in osteoporosis diagnostics and therapeutics.

In the final analysis, osteoporosis is a condition of bone, a complex tissue that undergoes physiologic repair throughout life. The study of bone transcends a simple measurement of its amount or mineral density to encompass aspects of its physical properties and geometry. This chapter introduces the reader to the "nature" of osteoporosis, *ie,* the physical characteristics of healthy and porotic bone. In addition, some of the important geometric features of bone that substantially influence bone strength are discussed. Finally, the gross and cellular features of normal and disordered bone remodeling are described. Bone modeling is a continuous renewal process that underlies the basis for changes in bone mass during adult life.

## Osteoporotic Bone

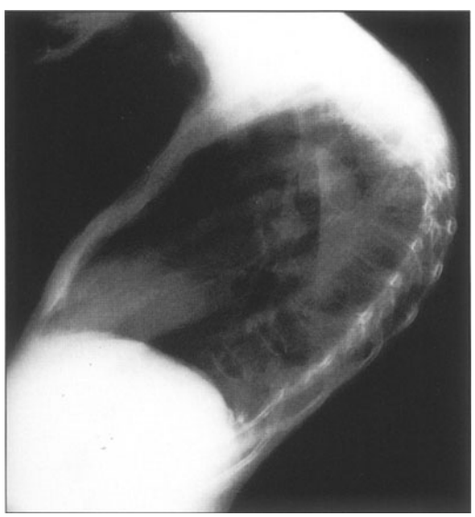


**FIGURE 1-1.** Lateral chest radiograph showing a classic spine deformity called kyphosis. Kyphosis is the end result of multiple vertebral compression fractures. *Osteoporosis* is defined as a skeletal condition of decreased bone quantity accompanied by abnormalities in the microscopic architecture of bone that renders a person more likely to sustain a fracture with little or no trauma. Osteoporosis frequently is considered in the context of specific fracture syndromes, including vertebral compression, Colles' (distal radial) fracture, and hip fracture. However, osteoporosis truly is a disease of global skeletal fragility, with increased risk of low-trauma fractures in all portions of the skeleton. (Copyright © R. Marcus.)

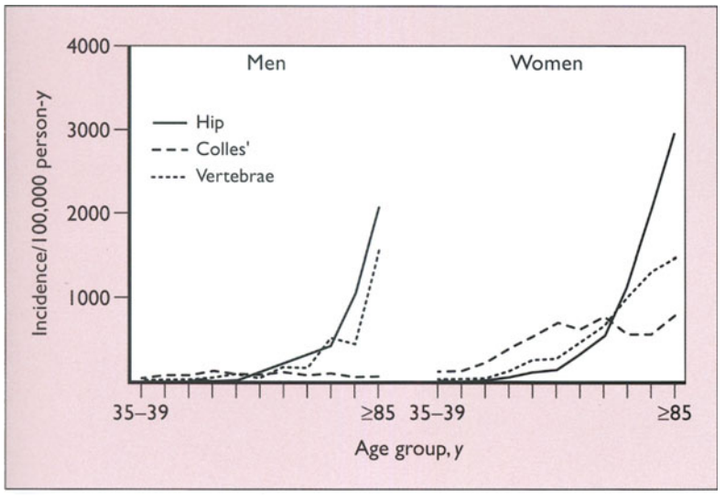



**FIGURE 1-2.** Incidence of osteoporotic fractures. The clinical consequence of bone fragility is fracture. Shown here are curves representing the age-related incidences of vertebral, forearm, and hip fractures in North American men and women. The incidence of fractures is about twice as great in women as it is in men. However, osteoporosis is not a disorder exclusively of women. The incidence of hip fracture is increasing most rapidly in men older than 70 years of age. One third of vertebral fractures result in pain sufficient to cause the patient to seek medical attention; however, many occur without obvious symptoms, becoming apparent only as a loss of height or development of curvature. Wrist fractures typically occur at an earlier age than do hip fractures. This fact is explained by differences in the types of falls that occur. Wrist fractures occur when a person standing upright falls forward and attempts to break the fall by arm extension. Hip fractures are more likely to occur when a person attempts to rise from a seated position but fails to generate adequate momentum to elevate the center of gravity to a stable position. A backward fall results, with direct impact on the femoral trochanter. Thus, the occurrence of fracture in patients with osteoporosis is a function not only of intrinsic bone strength but also of factors conducive to falls. (*Adapted from* Cooper and Melton [1].)

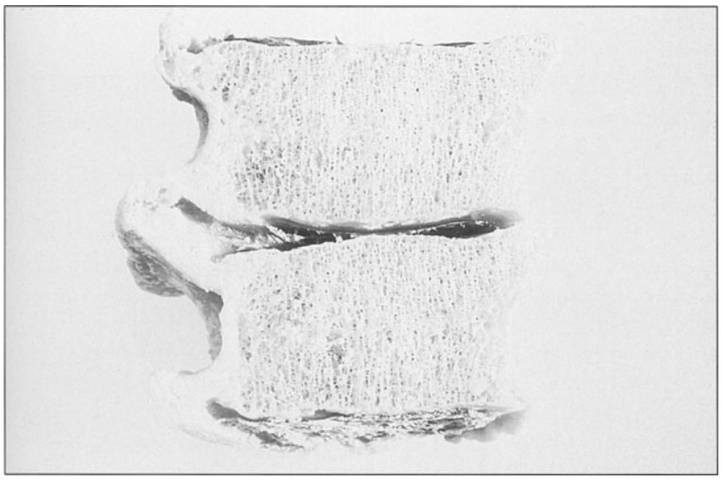


**FIGURE 1-3.** (*see* Color Plate) Normal vertebral bodies. Contained within a thin cortical shell, about 35% of vertebral bodies by weight and 80% by surface are composed of a honeycomb of vertical and horizontal bars, or trabeculae. In adults, trabecular interstices of the axial (central) skeleton constitute the primary repository of red bone marrow. Events leading to the loss of bone occur on bone surfaces. The surfaces of trabecular bone are great in extent and lie in close proximity to the marrow-derived cells that participate in bone turnover. Therefore, changes in bone mass occur earlier and to a greater extent than they do in regions of the skeleton that are primarily cortical. (Copyright © R. Marcus.)

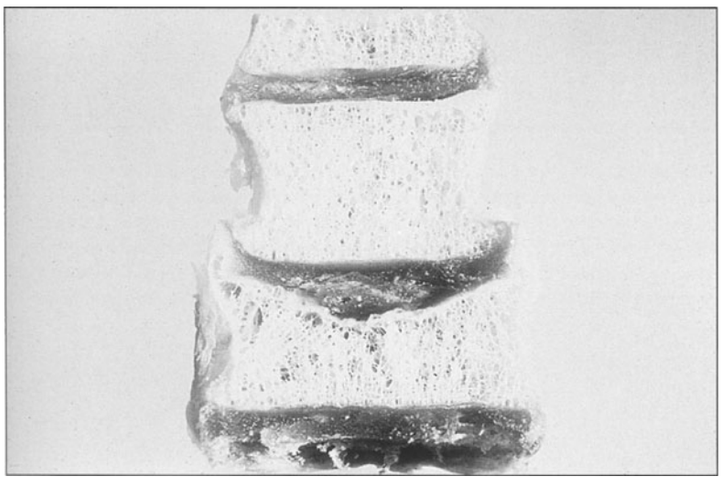


**FIGURE 1-4.** (*see* Color Plate) Osteoporotic vertebral bodies. The term *porosis* means spongelike. Weakness of the trabecular structure has resulted in mechanical failure, with collapse of the intervertebral disk into the underlying bony substance. This weakness reflects a decrease in the total amount of bone within the vertebral body and also a disruption of the normal trabecular micro-architecture, as evidenced by the appearance of several large holes. A formal definition of the term *osteoporosis* is a skeletal condition characterized by low bone mass and abnormal micro-architecture, leading to increased risk of fracture with minimal trauma. (Copyright © R. Marcus.)

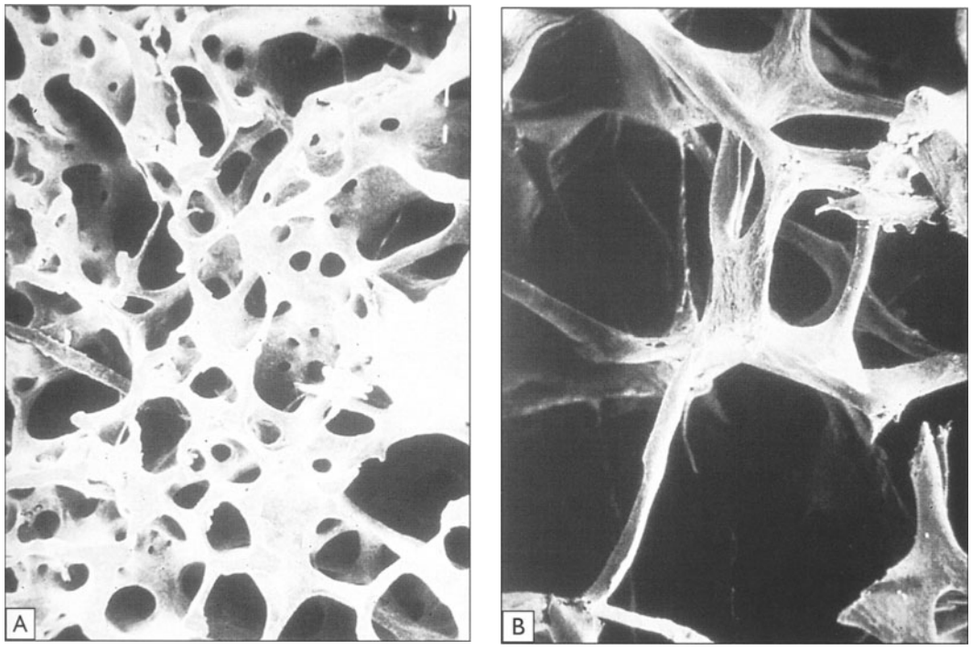



**FIGURE 1-5.** (see Color Plate) Scanning electron micrograph of normal (**A**) and osteoporotic (**B**) trabecular structures. In osteoporosis, the platelike normal trabeculae have been replaced by thin rods, and trabecular perforation has disrupted trabecular continuity. (*Courtesy of* J. Kosek.)

## Bone Mass Measurement

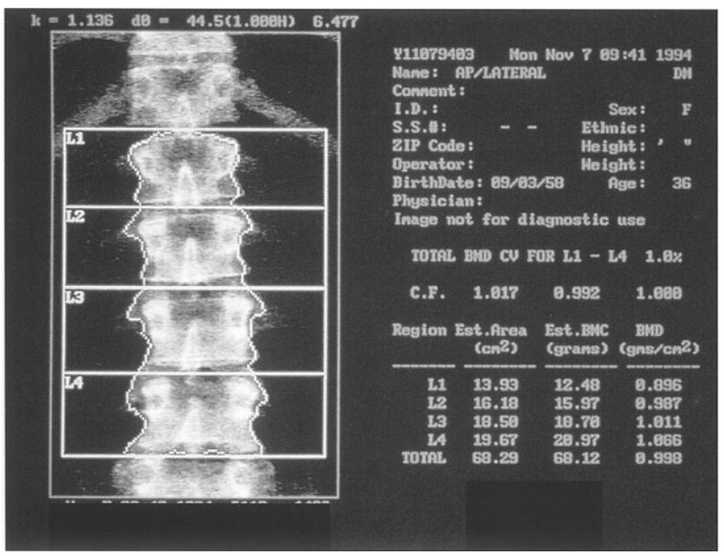



**FIGURE 1-6.** Printout from a lumbar spine bone density examination. Although low bone mass and architectural disruption are essential components of the diagnosis of osteoporosis, current widely applicable diagnostic tools provide measurements of bone mass (the amount of bone) only, and do not address micro-architectural disruption or other "qualitative" aspects of bone fragility. Dual-energy x-ray absorptiometry is a technique that exploits the ability of bone mineral to attenuate the passage of photons through the body to provide estimates of the mineral density of bone. Machine software estimates the area and mineral content of bones in the region scanned. A calculated areal bone mineral density (measured in $g/cm^2$) is generated for the scanned region. For clinical purposes, the scanned regions generally include the lumbar spine, proximal femur, forearm, and whole body. For research purposes, any skeletal region can be assessed.

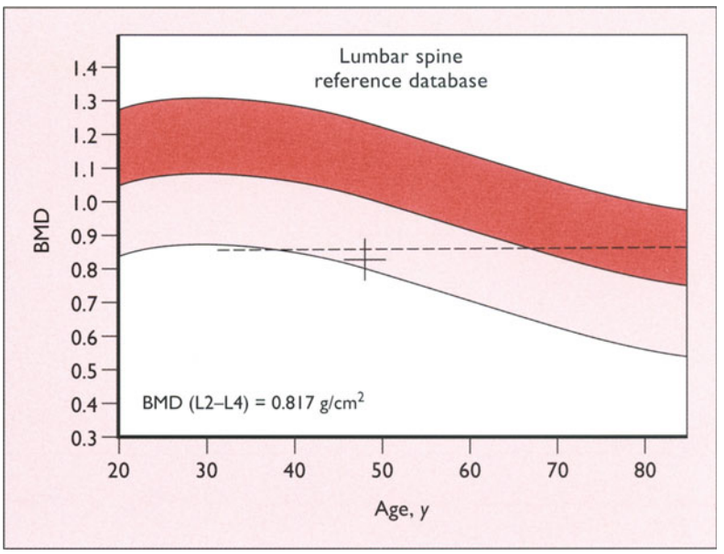



**FIGURE 1-7.** Bone mineral density (BMD) on dual-energy x-ray absorptiometry. Patient value (*dark area*) is superimposed on a graph representing the mean ±2 standard deviations for a healthy population. Normative data are gender-specific, and ethnicity-specific data are currently under development. In this case, the patient's value is almost 2 standard deviations below expectation for age.

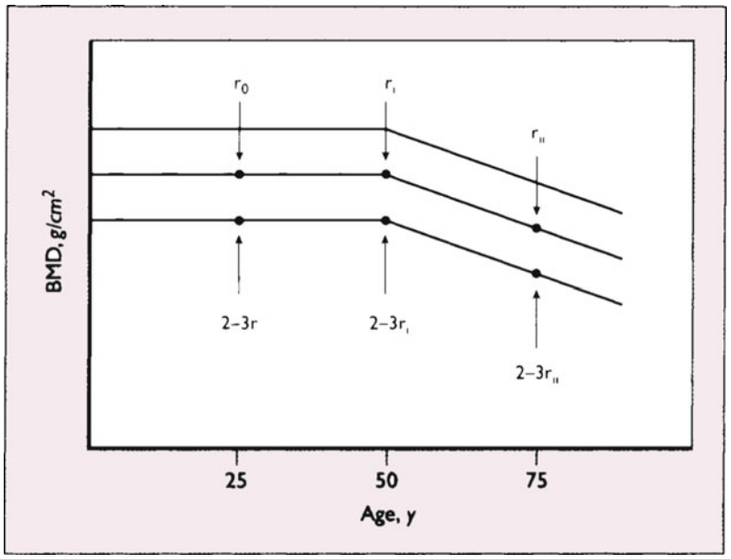



**FIGURE 1-8.** Implications of low bone mineral density (BMD). Based on prospective observational studies, it is estimated that each standard deviation below the age-predicted mean value imposes a two- to threefold increase in long-term fracture risk.

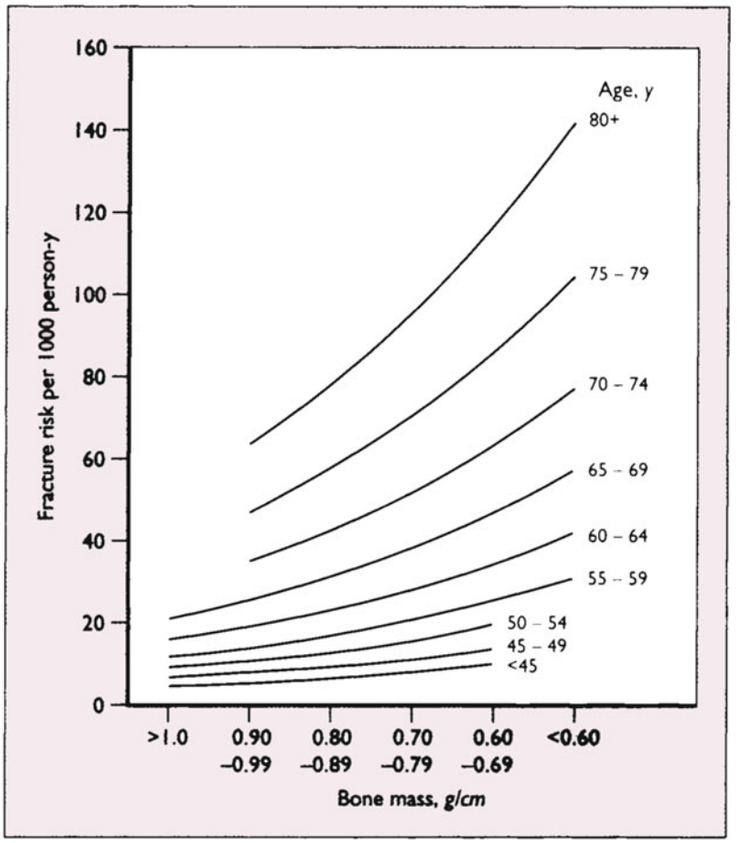



**FIGURE 1-9.** Interaction of age and bone mineral density (BMD) on fracture incidence. A large cohort of women were followed over time. Fracture incidence is shown on the vertical axis, and the women are stratified by bone density along the horizontal axis. In addition, women are stratified by age, represented by a family of curves. At any given BMD, fracture incidence is higher with progressive age. In fact, the slope of this relationship to fracture is steeper for age than it is for BMD, which would not be expected if BMD itself were the sole determinant of fracture risk. For the oldest women, the incidence of falls is greater and contributes to the added fracture experience. However, falls do not account for the age effect at younger ages. Thus, attention has been paid to so-called qualitative factors affecting bone fragility that are not accounted for in the BMD measurement. (*Adapted from* Hui *et al.* [2].)

## Qualitative Abnormalities in Osteoporotic Bone

**BONE QUALITY IN OSTEOPOROSIS**

- Altered mineral or matrix composition
- Cement lines
- Cortical porosity
- Fatigue accumulation
- Trabecular disruption

**FIGURE 1-10.** Qualitative abnormalities in osteoporotic bone are provided.

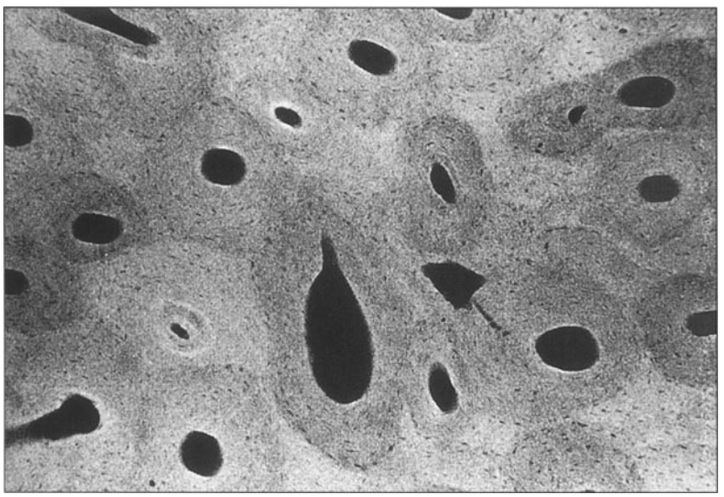


**FIGURE 1-11.** Microradiograph of qualitative abnormalities in osteoporotic cortical bone. Note the substantial heterogeneity of haversian canal dimensions. The gray levels indicate patchy differences in mineralization, with white representing the highest level [3].

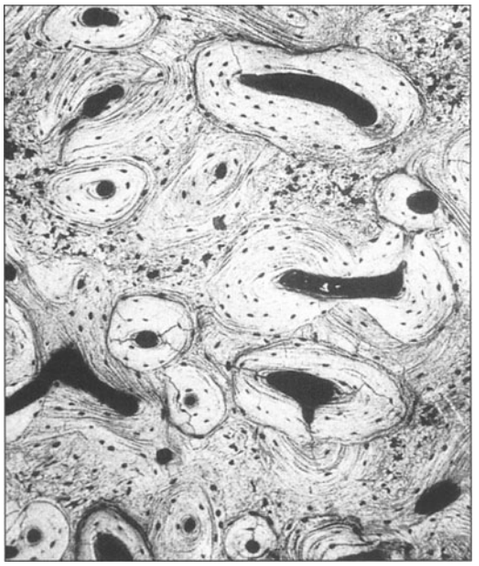
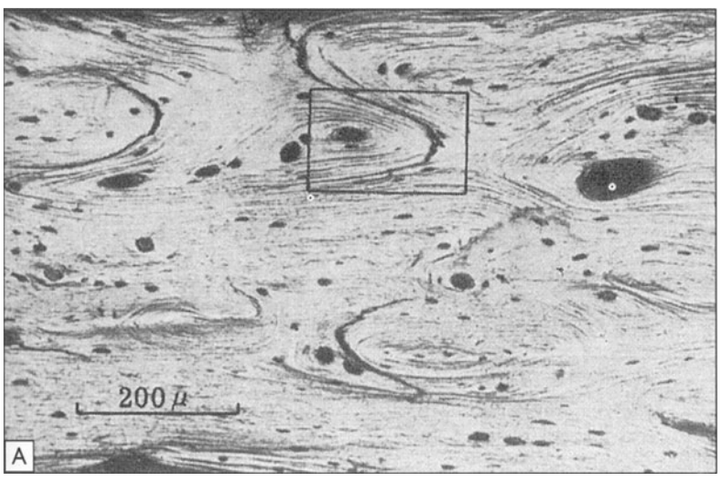


**FIGURE 1-12.** Micrograph of a biopsy specimen of the iliac crest showing qualitative abnormalities in bone. Cortical porosity is seen in this specimen from an 80-year-old man. Note the occurrence of large haversian canals in several osteons. Also note the very high prevalence of haversian systems, indicating an extensive lifelong history of remodeling events [4].



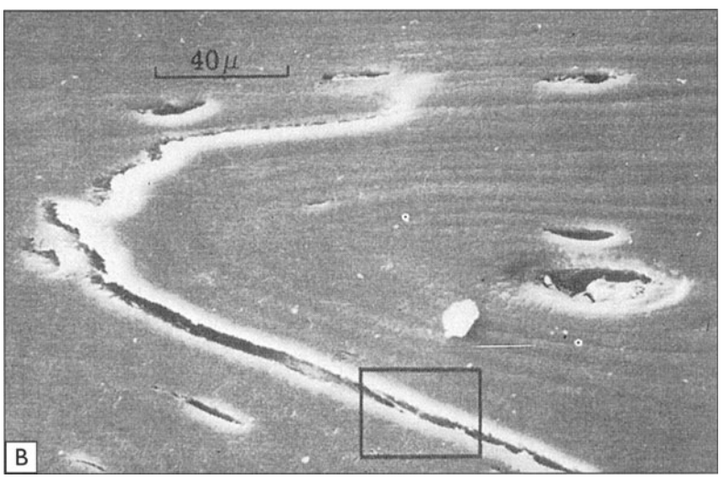




**FIGURE 1-13.** Micrograph of qualitative abnormalities in bone showing cement lines. Cement lines are the residue of a previous bone resorption event. Composed of a filigree of woven, rather than dense lamellar collagen, cement lines create an area of weakened resistance to structural failure.

**A,** Cement lines forming the base of osteonal units. **B,** Dehiscence of a cement line after application of a bending force to the whole bone. When bone fractures, fracture lines propagate from one cement line to the next [5].

# Bone Geometry

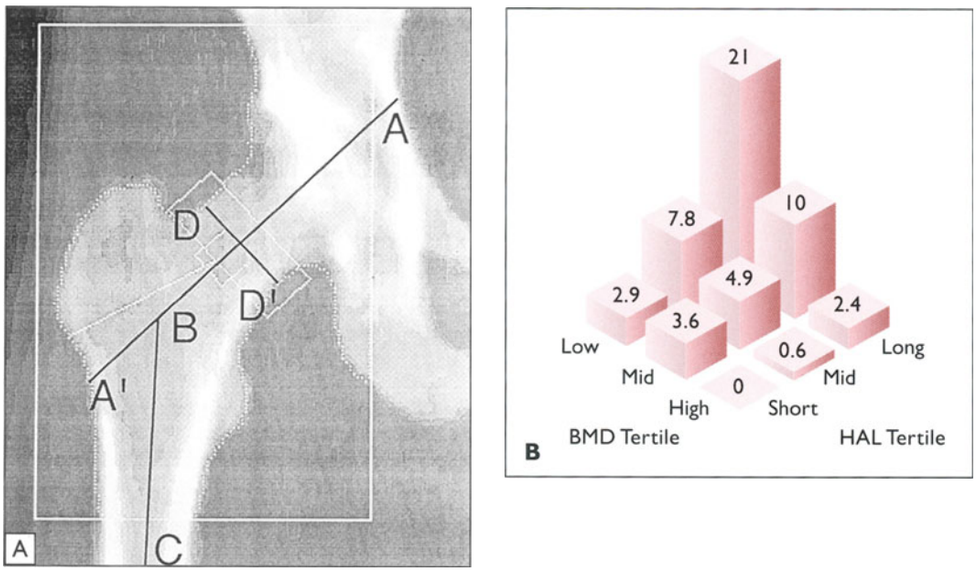



**FIGURE 1-14.** Geometric contributions to bone strength and fracture risk. Despite an undisputed relationship between bone mineral density (BMD) and fracture incidence, factors independent of BMD make important contributions to fracture. Of particular importance are bone geometry and the occurrence of falls (see Chapter 14). To illustrate the role of macroscopic bone geometry, these two figures show the important effect a measurement called the hip axial length (HAL) has on hip fracture risk. **A,** HAL is the length of a straight line connecting the inferior surface of the greater trochanter to the inner surface of the hip acetabulum. **B,** Results of a large prospective observational study of elderly women showing that the incidence of hip fracture is heavily dependent on HAL. At any level of BMD, women with longer HAL had significantly greater risk of hip fracture. Indeed, women with BMD in the lowest tertile who also had HAL in the longest tertile experienced a 21-fold increased relative risk of hip fracture. (*Part B adapted from* Faulkner *et al.* [6].)

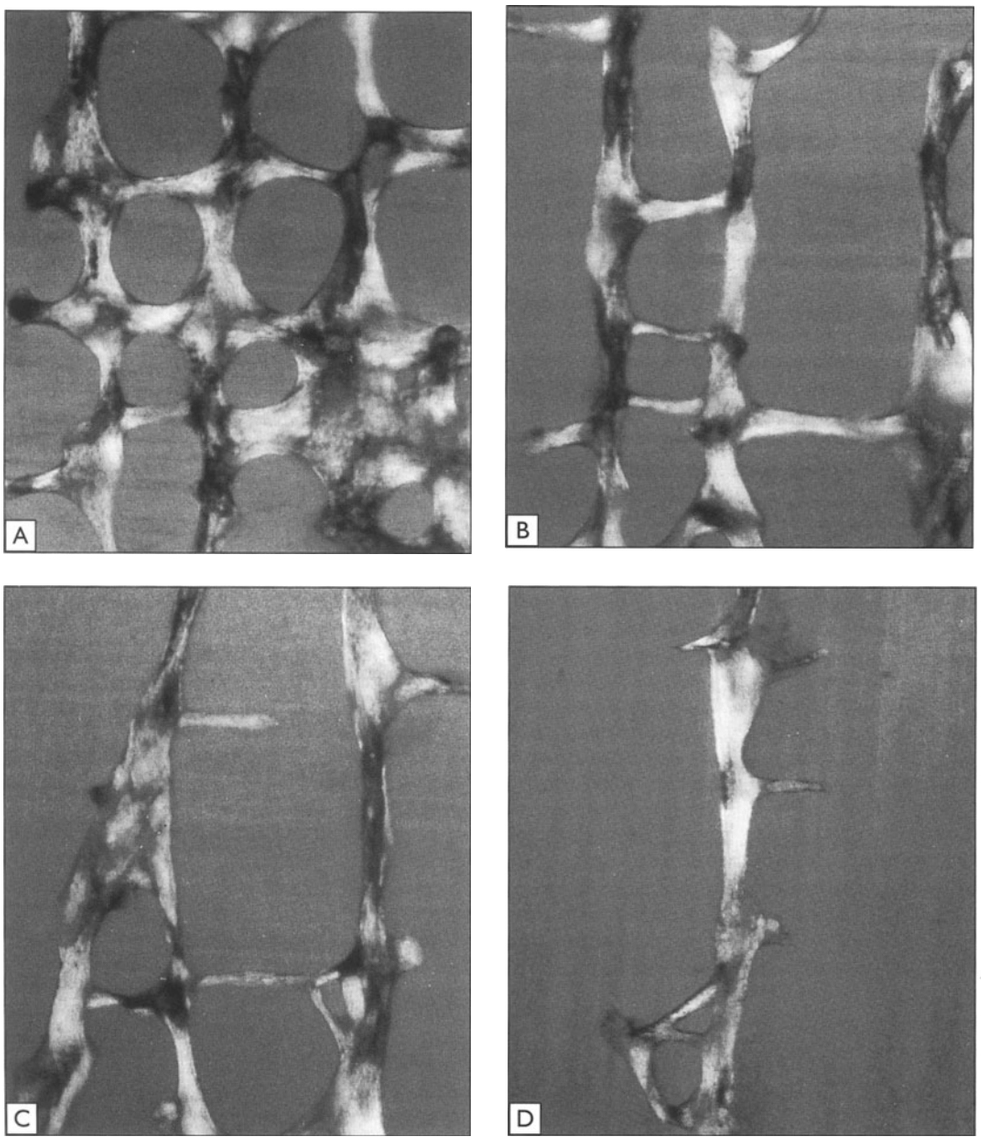



**FIGURE 1-15.** (see Color Plate) Geometric contributions to bone strength and fracture risk. Illustrated is the pattern of trabecular loss with age in which progressive loss of horizontal trabeculae is more exaggerated than is that of vertical trabeculae. The microscopic architecture is shown in a 50-year-old man (**A**), a 58-year-old man (**B**), a 76-year-old man (**C**), and an 80-year-old woman (**D**) [7].

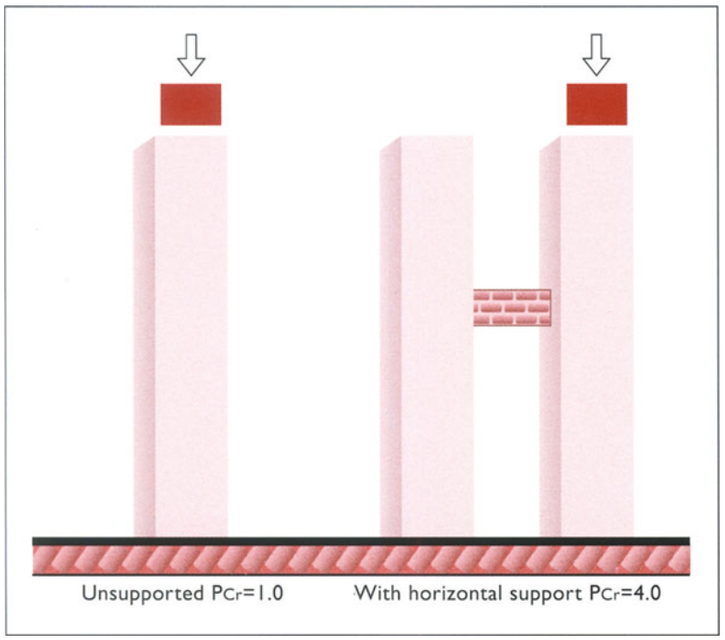



**FIGURE 1-16.** Diagram of geometric contributions to bone strength and fracture risk showing the consequences of horizontal trabecular loss. A single horizontal connecting strut increases by fourfold the maximum load (Pcr) that can be carried by a vertical bar without buckling. Thus, loss of horizontal trabeculae with age has a profound independent effect on vertebral trabecular strength. (*Adapted from* Snow-Harter and Marcus [8].)

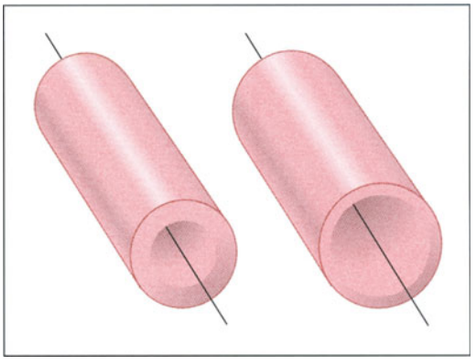


**FIGURE 1-17.** Diagram of geometric contributions to bone strength and fracture risk showing the effect of mass distribution on bone strength. Assume that two cylinders have equal mass. The one on the right shows the distribution of mass farther away from the bending axis, *ie,* increased cross-sectional moment of inertia (CSMI), resulting in substantially increased resistance to bending along this axis. The long bones of men are generally larger than those of women. Therefore, the increased CSMI of the bones of men confers on them relative protection against fracture at any given value of bone mineral density. One adaptive response that occurs with aging is a compensation for bone loss by increasing the CSMI of the long bones, a process that appears to be more efficient in men than it is in women. (*Adapted from* Snow-Harter and Marcus [8].)

## Role of Remodeling in Lifelong Acquisition and Loss of Bone

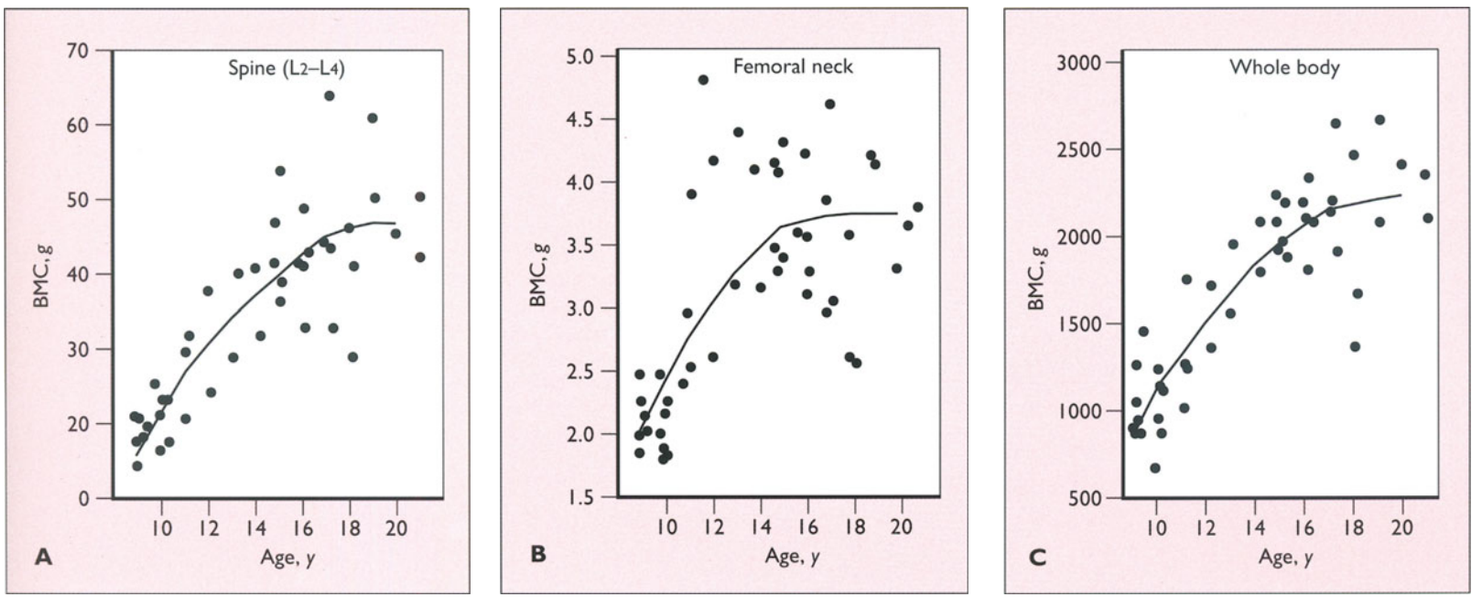



**FIGURE 1-18. A–C,** Acquisition of bone during adolescence. At any time during adult life, bone mass reflects bone that has been gained during years of growth minus bone that subsequently has been lost. Previous theories about osteoporosis have not adequately considered the role of bone acquisition in determining lifelong fracture risk. This study of healthy white girls aged 9 to 21 years shows that about 60% of final adult "peak" bone mass is acquired during the adolescent growth spurt. Only about 5% of peak bone mass is acquired after age 18 years. Thus, adolescence constitutes a window of opportunity when genetic, dietary, hormonal, and other factors determine the magnitude of bone gain. About 80% of peak bone mass is genetically determined. Important environmental factors include dietary calcium intake, reproductive endocrine status, and habitual physical activity. In contrast, adolescence is a window of vulnerability when inadequate attention to these same factors can lead to low bone mass at skeletal maturity. Persons who have not gained adequate bone mass would not need to lose very much bone in adulthood to have a substantially increased risk of osteoporosis and fracture. Of particular concern are dietary calcium intake, which is generally low in American teenaged girls; a relatively sedentary lifestyle; and the high prevalence of anorexia nervosa and other eating disorders. (*Adapted from* Katzman *et al.* [9].)

**ACQUISITIONAL OSTEOPENIA**

- Delayed puberty
- Immobilization or therapeutic rest
- Specific disorders
  - Anorexia nervosa
  - Cystic fibrosis
  - Intestinal or renal disease
  - Marfan syndrome
  - Osteogenesis imperfecta

**FIGURE 1-19.** Acquisitional osteopenia. This is a partial list of childhood conditions known to occur in adults with low bone mass. Low bone mass puts adults at increased risk for fracture.

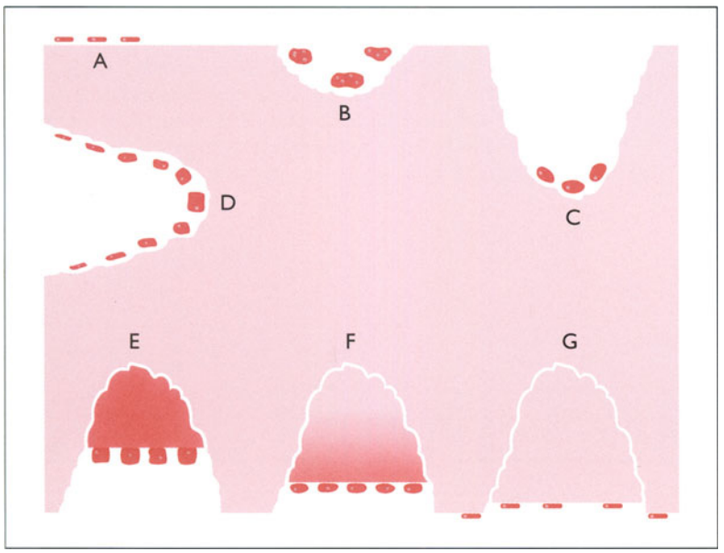



**FIGURE 1-20.** Bone remodeling. Once new bone is laid down, it is subject to a continuous process of breakdown and renewal called *remodeling* that continues throughout life. After linear growth stops and peak bone mass has been reached, remodeling constitutes the final common pathway by which bone mass is adjusted throughout adult life. Remodeling is carried out by thousands of individual and independent "bone remodeling units" on the surfaces of bone throughout the skeleton.

**A,** About 90% of bone surface is normally inactive, covered by a thin layer of lining cells. **B,** In response to physical or biochemical signals, recruitment of marrow precursor cells to a site at the bone surface results in their fusion into the characteristic multinucleated osteoclasts that resorb, or dig a cavity into, the bone. In cortical bone, resorption creates tunnels within haversian canals, whereas trabecular resorption creates scalloped areas of the bone surface called Howship lacunas. **C,** On termination of the resorption phase, a 60 μm cavity remains and is bordered at its deepest extent by a cement line, a region of loosely organized collagen fibrils. **D,** Completion of resorption is followed by ingress of preosteoblasts derived from marrow stromal stem cells into the base of the resorption cavity. **E,** These cells develop the characteristic osteoblastic phenotype and begin to replace the resorbed bone by elaborating new bone matrix constituents, such as collagen, osteocalcin, and other proteins. **F,** Once the newly formed osteoid reaches a thickness of about 20 μm, mineralization begins.

The remodeling cycle normally is completed in about 6 months (**G**). No net change in bone mass occurs as a result of remodeling when the amount of resorbed bone replaced equals the amount removed. Persistence of small bone deficits on completion of each cycle, however, reflects an inefficiency in remodeling dynamics. Lifelong accumulation of remodeling deficits underlies the phenomenon of age-related bone loss. (*Adapted from* Marcus [10].)

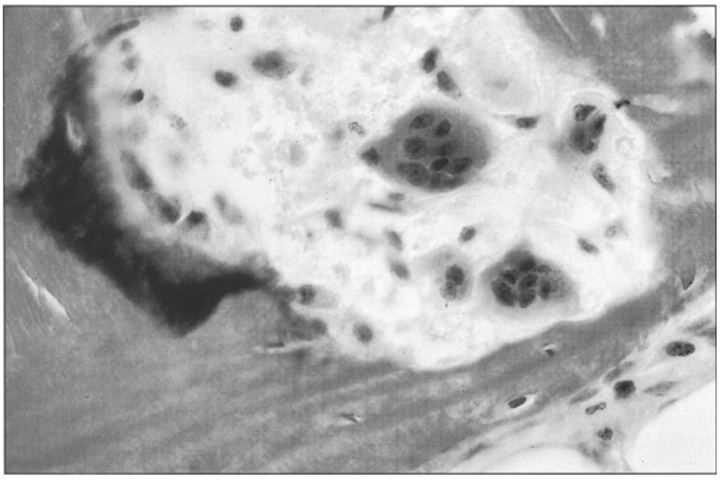


**FIGURE 1-21.** (see Color Plate) Bone biopsy specimen from the iliac crest showing the cellular participants in bone remodeling. Large multinucleated cells seen in the middle of the field are osteoclasts. Derived from a mononuclear macrophage precursor, these cells migrate to a locus on the bone surface, become adherent to the surface with participation of a number of adherence molecules, and resorb bone (both organic matrix and mineral). The layer of cuboidal mononuclear cells at the bone surface are osteoblasts, and the thick red band beneath them represents organic matrix that has not yet been mineralized (osteoid). Mineralized bone is olive in color (Goldner stain). (*Courtesy of* J. Kosek.)

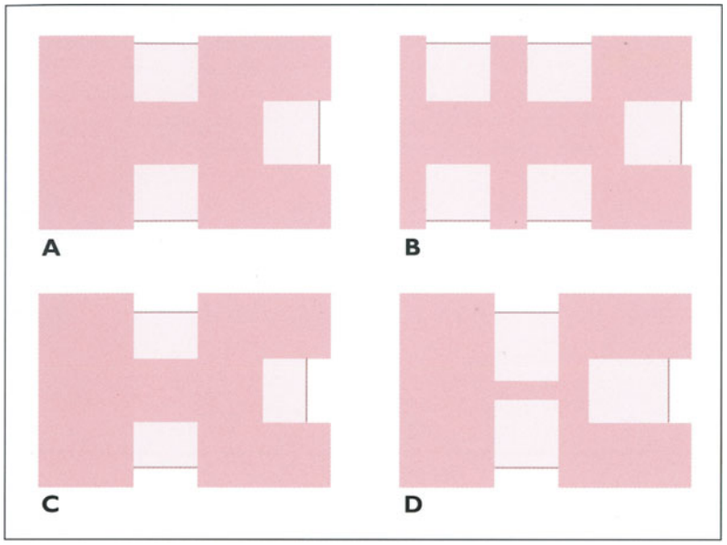



**FIGURE 1-22.** Perturbations in remodeling. Alterations in remodeling activity represent the final pathway through which diverse stimuli such as dietary insufficiency, hormones, and drugs affect bone balance. A change in the whole-body remodeling rate can be brought about through distinct perturbations in remodeling dynamics.

A representation of normal remodeling is shown. **A,** Three areas of remodeling activity, each with identical resorption lacunas that have filled in with new bone (*shaded area*). Identical small bone deficits are shown with each remodeling area, reflecting remodeling inefficiency (described previously). **B,** Increased remodeling owing to an increase in the activation, or birthrate, of remodeling units. Examples include hyperthyroidism, hyperparathyroidism, and hypervitaminosis D. **C,** Exaggerated inefficiency of osteoblastic response. The number of remodeling units in play is unchanged; however, the magnitude of bone deficit is increased. Such changes are typical of osteoblastic toxins, such as ethanol, and glucocorticosteroids. Progressive age may also be associated with increasing deficits in osteoblast recruitment and function. **D,** Exaggerated osteoclastic activity. Estrogen deficiency may augment osteoclastic resorptive capacity. If the resorption cavities perforate the trabeculae, no scaffold remains for new bone formation to take place. Such resorption becomes a permanent loss of bone.

At any given time, a transient deficit in bone exists, called the *remodeling space*, which represents sites of bone resorption that have not yet been filled. In response to any stimulus that alters the birthrate of new remodeling units, the remodeling space will either increase or decrease accordingly until a new steady state is established. This adjustment is seen as an increase or decrease in bone mass. (*Adapted from* Marcus [10].)

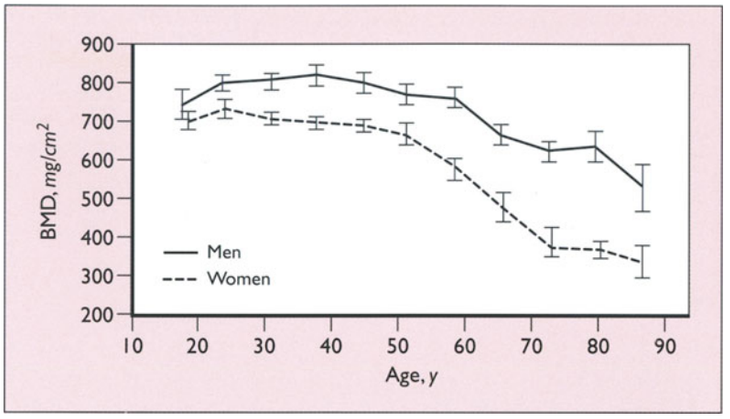



**FIGURE 1-23.** Age-related bone loss. This graph represents a large cross-sectional study of cortical bone mineral density (BMD) in men and women across the adult lifespan. At any time in adult life, BMD in men is higher than it is in women. However, this fact represents an artifact of bone size, which is larger in men. If 1-cm cubes of bone from average young men and women were compared, mineral content would be equal. It is not trivial that bone diameters in men are larger than those in women because bone strength is a function of BMD squared times the bone cross-sectional area. Thus, with bones of equal true BMD, larger cross-sectional areas confer relative protection against fracture on men (*see* Fig. 1-17).

Bone mineral density remains stable until about age 50 years, when both men and women show progressive loss. BMD loss is more rapid in women aged 50 to 60 years, reflecting the impact of menopausal loss of estrogen production. Subsequently, age-related losses of BMD are similar for men and women. Although bone loss detectable by densitometric methods is generally detected only after 50 years of age, more sensitive methods (albeit invasive, such as iliac crest biopsy) show the beginning of age-related bone loss as early as the third decade [7].

The maintenance of bone mass throughout adult life requires meeting a number of challenges imposed by both physiologic and environmental factors. From the principles of bone remodeling, discussed previously, it can be seen that any factors tending to increase overall bone remodeling will promote bone loss, whereas factors that reduce remodeling activity may lower the rate of bone loss. Listed are only a few of the important factors that may promote bone remodeling and bone loss in elderly persons: loss of reproductive function in all women and in a sizable number of elderly men; age-related increases in circulating parathyroid hormone, which may reflect a decreased calcium nutritional state either from limited nutrient intake or age-imposed deficits in vitamin D status and intestinal calcium absorption efficiency; and age-related decrease in habitual physical activity and recreational exercise. (*Adapted from* Meema and Meema [11].)

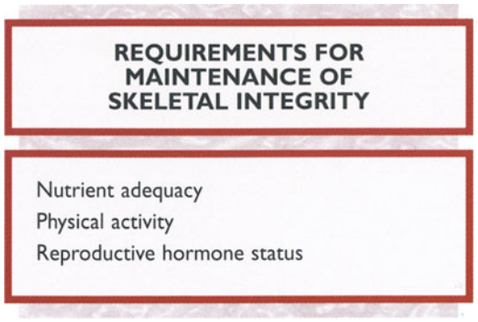



**FIGURE 1-24.** Requirements for maintenance of skeletal integrity. Skeletal integrity requires adequacy of habitual mechanical environment (physical activity), reproductive hormone status, and nutrients. Overzealous attention to any two of these factors does not suffice when the third factor is neglected. Thus, an immobilized patient loses bone even when both reproductive hormone and nutritional status are more than adequate. Similarly, a woman athlete who exercises to the point of development of amenorrhea (and low estrogen status) loses bone, despite a high mechanical environment and calcium supplementation.

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2

# Bone Acquisition and Peak Bone Mass

Laura K. Bachrach

The foundation of bone health is established in the first three decades of life [1]. Peak bone mass, acquired by early adulthood, serves as the bone bank for the remainder of adult life. The more robust the skeletal mass at its peak, the greater the amount of bone loss (from aging, menopause, and other factors) that can be tolerated without clinical signs of osteoporosis. The pace of bone mineral acquisition is similar to that of linear bone growth, with rapid gains in infancy, slower increases during childhood, and major gains at puberty [2]. Approximately half of peak bone mass is gained during the teenage years, making this a critical period for optimizing conditions for skeletal health. Unlike growth patterns, however, peak bone mineral acquisition lags 8 months behind peak height velocity [3]. Furthermore, gains in bone mineral continue into the third decade after bone growth has ceased [4].

Bone mineral acquired by early adulthood is a key determinant of the lifetime risk of osteoporosis. Peak bone mass accounts for at least half of the variability in skeletal mass in the elderly, with the remainder attributable to subsequent bone loss [1]. Largely, peak bone mass is predetermined by heritable factors. Family and twin studies suggest that 60% to 80% of the differences in peak bone mass between individuals can be attributed to genetics [5,6]. Ethnic and racial differences in bone mass have also been observed [7]. Although some of these differences appear to be artifacts of densitometry technique, healthy blacks have been shown to achieve greater true bone density than nonblacks during adolescence [8,9]. The gene or genes linked to osteoporosis have not yet been identified, although several have been considered, including the vitamin D and estrogen receptors [10].

Lifestyle factors also have a substantial influence on bone acquisition, accounting for 20% to 40% of the variability in young adult skeletal mass. Maximal bone mineral gains occur only when nutrition, physical activity, and hormone production are adequate. Body mass, especially the fat-free component, is a consistent correlate of bone mineral density in healthy youths [11–13]. The positive relationship between weight and bone mineral density may reflect common genetic determinants, overall nutritional status, or the effects of mechanical loading on the skeleton [13]. Calcium intake also influences rates of bone accrual as shown in several calcium supplementation trials; children given added calcium gained more bone mineral than did those in the control group [14,15]. The recommended daily calcium intakes for children and adolescents were increased in 1997, reflecting these findings [16]. Weight-bearing physical activity also can stimulate bone mineral accrual, and may modify bone size in some instances [3,17–19]. Several studies have shown that children and adults who are more active may gain 5% to 17% more bone mineral than do their sedentary peers [3,19]. Other studies have failed to find a correlation between exercise patterns and bone mass. For this reason, the amount and type of activity needed to foster bone accrual remains controversial. Furthermore, activity may boost bone acquisition only when calcium intake is sufficient [20]. Normal endocrine function also is necessary for optimal bone mineral acquisition. Bone mass in adolescents is more highly correlated with pubertal stage than with chronologic age, reflecting the pivotal role of sex steroids in bone accrual [21]. Peak bone mass is reduced in patients with sex steroid deficiency or resistance [22]. Growth hormone deficiency, hyperthyroidism, and glucocorticoid excess have also been associated with low bone mass in children as well as in adults [23–26].

The annual cost of treating osteoporotic fractures already has reached $13.8 billion, an amount that is projected to double over the next 25 years [27]. Stemming the rise of these costs will require effective intervention directed at increasing peak bone mass and reducing subsequent bone loss. A bone health program for all youths includes maintaining adequate body weight, appropriate calcium intake, and regular physical activity. Unfortunately, the gap between the recommended and the actual intakes of calcium in the United States continues to widen; more than 90% of girls and 50% of boys consume less than the optimal amount of calcium during the teen years [28]. In addition, American youths have become less active over time; only half of teens (aged 12 to 21 years) exercise vigorously on a regular basis, and 25% report no vigorous physical activity [29]. Girls are less active than boys, and black girls are less active than are white girls. Skeletal health is an immediate concern in youths with a variety of chronic disorders that have been associated with early deficits in bone mass [23]. Anorexia nervosa, exercise-associated amenorrhea, cystic fibrosis, and steroid-dependent disorders can reduce gains or accelerate loss of bone mineral, resulting in low bone mass for age. In severe cases of skeletal fragility, bone fractures can occur with minimal or no trauma, a condition termed *osteoporosis*. Whether deficits in bone that develop in childhood can be reversed with prompt recognition and treatment remains uncertain. Continued efforts are needed to define ways of optimizing peak bone mass and to deliver the message that osteoporosis prevention begins in childhood.

# Bone Mineral Acquisition

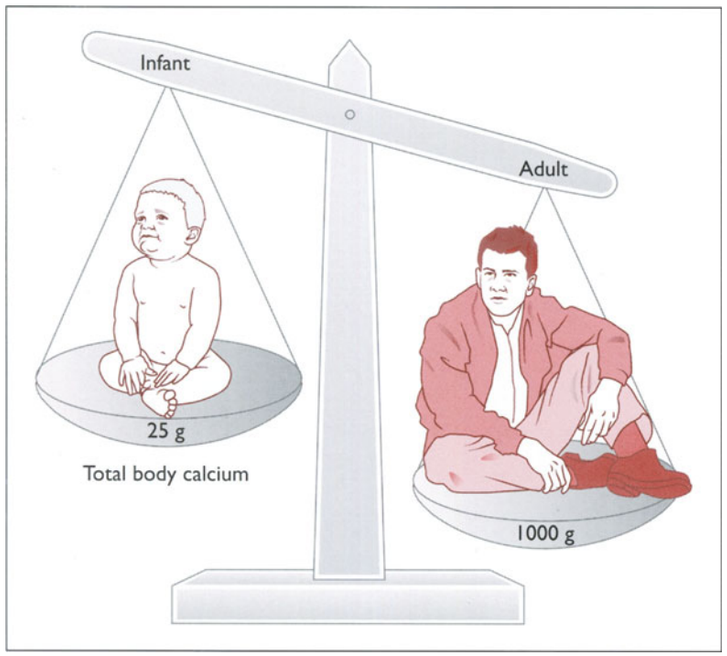
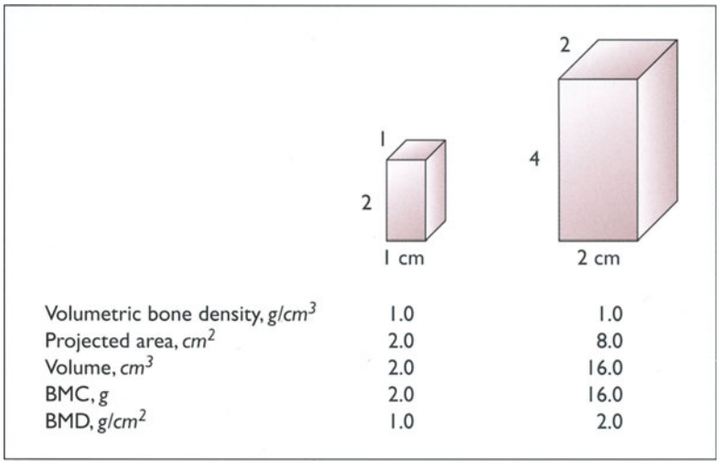



**FIGURE 2-1.** Accrual of bone mass during childhood and adolescence. Total skeletal calcium increases dramatically from infancy until adulthood. Half of these gains occur during adolescence, making this period critical in establishing bone health [2,3]. Peak bone mass is reached during the third decade and serves as the bone bank for the remainder of adult life [4,30].




| | | |
|---|---|---|
| Volumetric bone density, $g/cm^3$ | 1.0 | 1.0 |
| Projected area, $cm^2$ | 2.0 | 8.0 |
| Volume, $cm^3$ | 2.0 | 16.0 |
| BMC, $g$ | 2.0 | 16.0 |
| BMD, $g/cm^2$ | 1.0 | 2.0 |

**FIGURE 2-2.** Noninvasive measurement of bone mineral. Dual-energy x-ray absorptiometry (DXA) is the most commonly used means of determining bone mineral content (BMC, measured in g) and bone mineral density (BMD, measured in $g/cm^2$). DXA corrects for the area but not the thickness of bone in the region studied. BMC and BMD are influenced by bone size. The two blocks have the same material properties (or volumetric density); however, the reported BMC and BMD are greater in the larger block. Models of volumetric bone density (bone mineral apparent density, BMAD, or BMDvol) have been developed to reduce the influence of bone size on bone mineral measurements [31,32]. BMAD (in $g/cm^3$) is useful in distinguishing between gains in bone size and increases in volumetric bone density during childhood and adolescent growth. (*Adapted from* Carter *et al.* [31].)

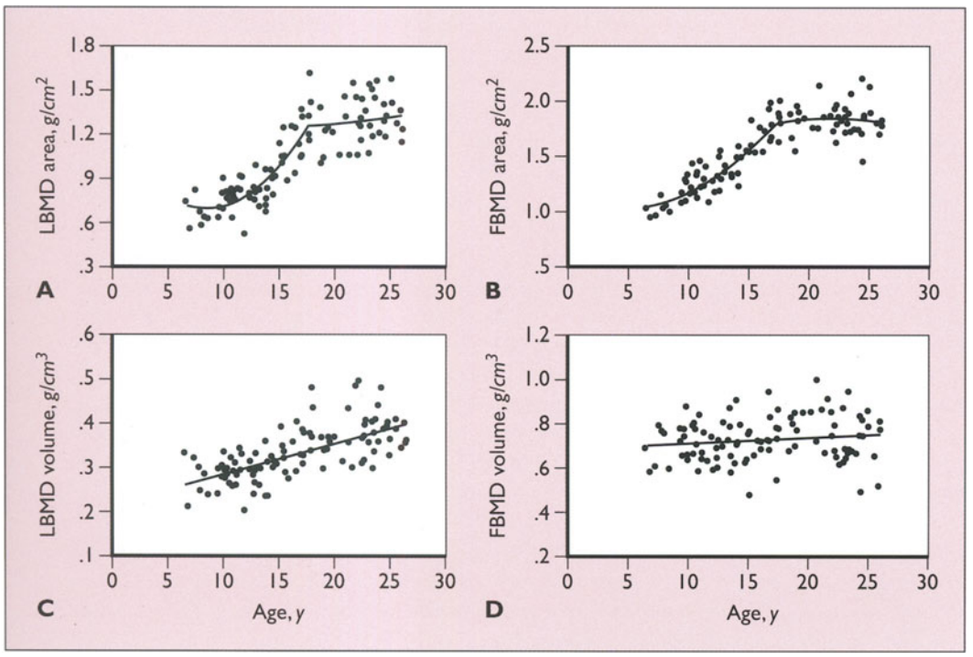



**FIGURE 2-3.** Bone mineral acquisition and bone growth. Gains in bone mineral during childhood and adolescence vary by skeletal site and the measurement term used [32–35]. **A** and **B,** Areal bone density (BMD area) increases with age at all sites, including the lumbar spine (L) and femoral shaft (F). **C** and **D,** In contrast, volumetric bone density (BMD volume) increases at the spine but not at the femoral shaft. These findings suggest that gains in bone mass during adolescence are due largely to bone expansion, although trabecular bone mass within the vertebrae increases as well [35]. Data from healthy boys are shown; similar differences in areal and volumetric BMD are observed in girls [32]. (*Adapted from* Lu *et al.* [32].)

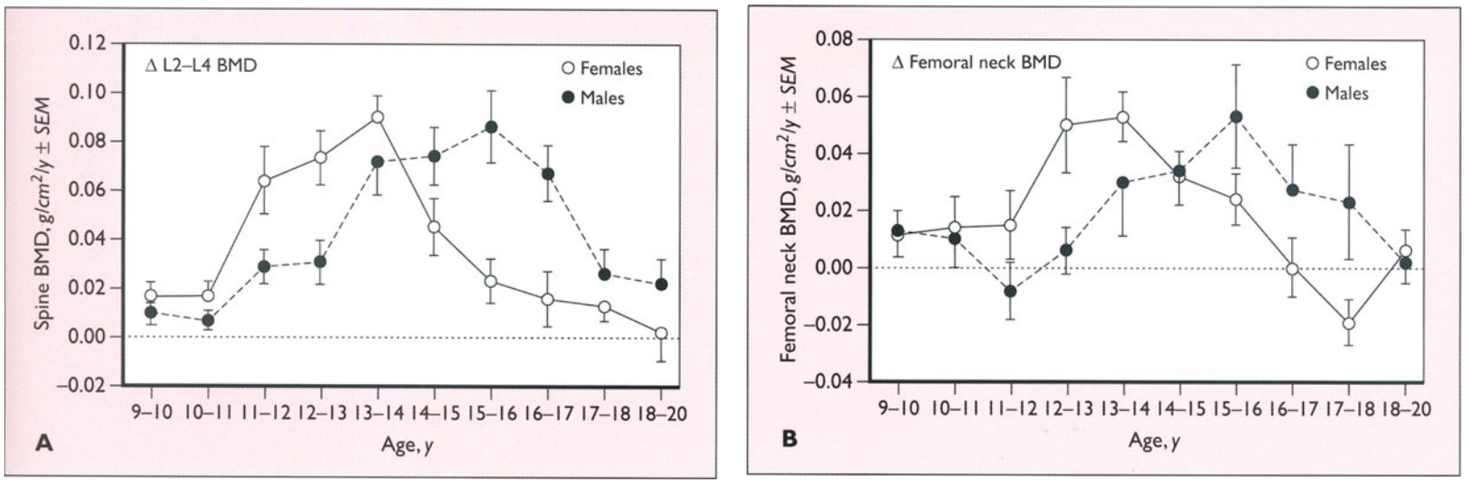



**FIGURE 2-4.** Bone mineral acquisition during puberty. The tempo of bone mineral acquisition during adolescence is more closely linked to pubertal development than to chronologic age [2,3]. Spine (L2–4)(**A**) and femoral neck (**B**) bone mineral density (BMD) increase most rapidly between the ages of 11 and 14 years in girls and 14 and 17 years in boys, reflecting the later onset of puberty in boys [30]. Gains in BMD are greater at the spine and hip than they are in the forearm or shaft of the femur. Girls reach 95% of their adult bone mineral content by the age of 18 years and have only modest gains during the third decade of life [4,36]. (*Adapted from* Theintz *et al.* [30].)

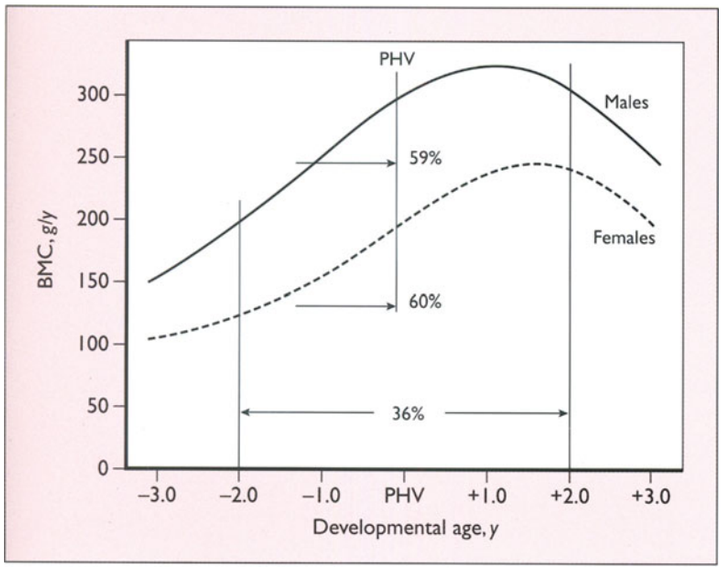



**FIGURE 2-5.** Bone mineral acquisition lags behind linear growth. The most rapid gains in total body bone mineral content (BMC) occur approximately 0.7 year after peak height velocity (PHV) is reached [3]. At the age of PHV (11.6 years of age for girls and 13.5 for boys), adolescents have reached 90% of adult height but only 60% of adult total body BMC, 60% of adult BMC for the spine, and 70% of adult BMC at the femoral neck. The discrepancy between bone size and mineral content during the adolescent growth spurt results transiently in relative bone weakness, possibly contributing to the higher incidence of fracture at this age [37]. (*Adapted from* Bailey [38].)

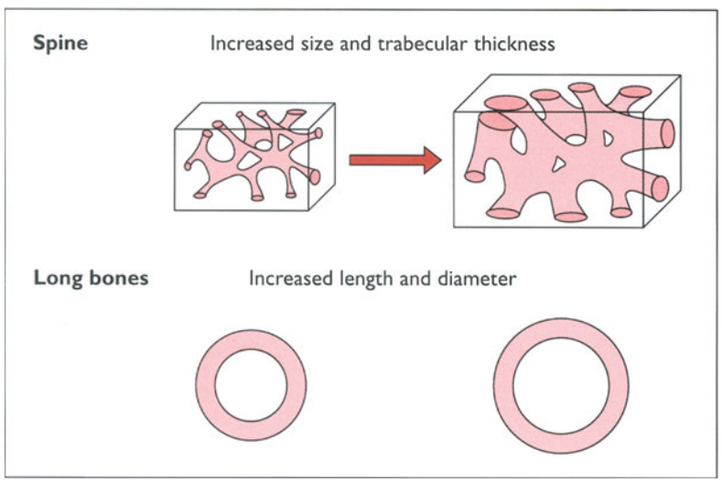



**FIGURE 2-6.** Adolescent changes in bone geometry. Changes in bone geometry accompany gains in bone size and mineral throughout childhood as the medullary cavity expands. Spinal vertebrae increase not only in size but also in the thickness of trabeculae within the bone [35]. Long bones increase in length and in cross-sectional area. The increases in cortical thickness are largely proportional to the increase in bone diameter, so volumetric bone density of long bones changes little throughout childhood and adolescence [35]. Hip axial length (HAL) increases during puberty; however, the ratio of HAL to height does not change [39]. These skeletal changes are important clinically because bone size and shape influence bone strength, independent of bone mineral content [40,41]. (*Adapted from* Seeman [35].)

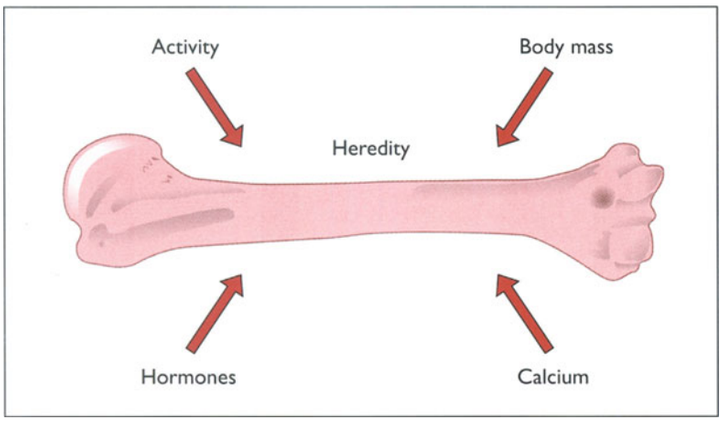
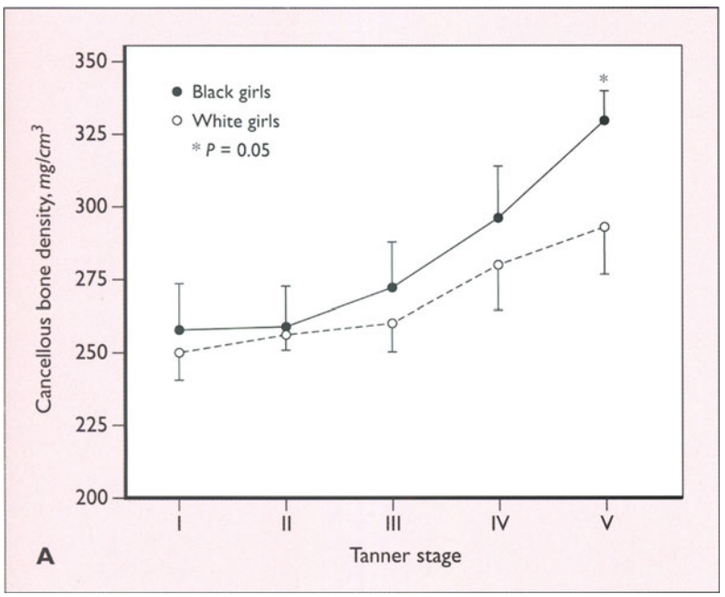
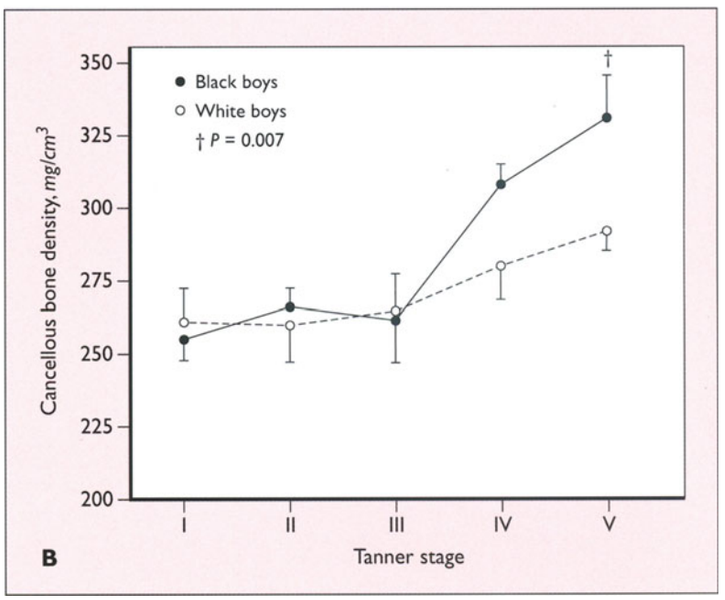
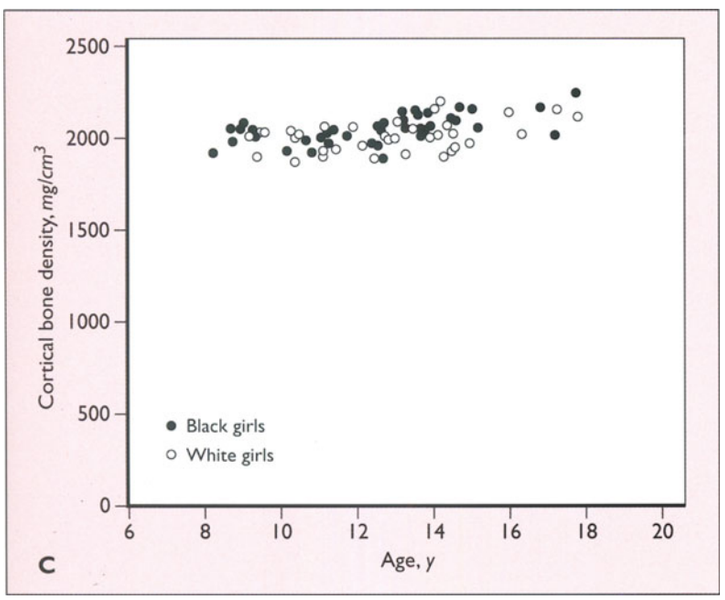



**FIGURE 2-7.** Determinants of peak bone mass. Peak bone mass is largely determined by genetic factors, which account for 60% to 80% of the observed variance in adult bone mineral [5,6]. Several lifestyle factors influence the remaining 20% to 40%. Weight-bearing physical activity stimulates bone accrual, whereas immobility leads to accelerated bone loss [3,18]. Body mass is highly correlated with bone mass, perhaps because weight reflects bone size and nutritional status [11,13]. Additionally, body weight may act as a mechanical load to the skeleton [13]. The lean mass component of total body weight is associated more highly with bone mass than is total body fat mass [12]. Calcium intake modifies rates of bone gain and resorption [14,15]. Finally, sex steroids and growth hormone contribute to bone mineral accrual, whereas glucocorticoids, thyroid hormone, and parathyroid hormone in excess may result in bone loss [22–26].



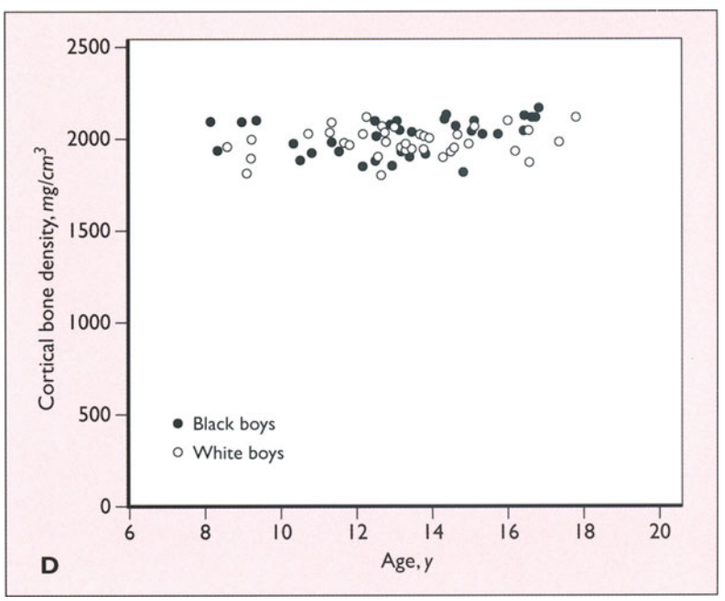




**FIGURE 2-8.** Racial differences in bone mass. There are few racial differences in bone mass between Asians, Hispanic, and white youths once adjustments are made for bone size [39–42]. By late adolescence, however, black youths have significantly greater bone mass than do white youths [8]. Using quantitative computed tomography, Gilsanz *et al.* [8] found racial differences in bone density, but not bone size, at the spine (**A** and **B**). In contrast, bone density at the femoral shaft (**C** and **D**) did not differ by race; however, blacks had greater cross-sectional area at that site than did whites. The observed differences in bone density and size probably contribute to the lower incidence of osteoporosis in blacks [7]. (*Adapted from* Gilsanz *et al.* [8].)

**CANDIDATE GENES FOR OSTEOPOROSIS**

| Gene | Role in Bone Metabolism | Polymorphisms |
|---|---|---|
| Vitamin D receptor | Vitamin D acts through its receptor to influence calcium absorption, bone differentiation, and mineralization | *BsmI/ApaI/TaqI*. Intronic polymorphisms, function unknown; *FokI* alters VDR translational start site and receptor protein size |
| Estrogen receptor | Estrogen acts through its receptor to influence skeletal growth, maturation, and bone loss after menopause | *PvuII/XbaI* intronic polymorphism, function unknown |
| Collagen I α I | Major protein in bone; mutations occur in type I collagen genes in osteogenesis imperfecta | COL1A1 polymorphism, function unknown |
| Transforming growth factor | Present in bone matrix; may regulate osteoblast-osteoclast coupling | Polymorphism, function unknown |
| Interleukin 6 | Regulates osteoclast growth and differentiation; may mediate effects of sex steroids on bone | Polymorphism, function unknown |

**FIGURE 2-9.** Candidate genes for osteoporosis. Heritable factors are major determinants of peak bone mass, explaining an estimated 60% to 80% of the variability in peak bone mass between individuals [5,6]. Racial, ethnic, and familial similarities in bone mineral density have been observed, supporting the contribution of genetics in bone acquisition. The osteoporosis gene or genes have not yet been identified [10]. The genes listed have been considered as candidates because gene polymorphisms have been associated with bone mass or the gene product plays a role in bone metabolism, or for both reasons. VDR—vitamin D receptor. (*Adapted from* Hobson and Ralston [10].)

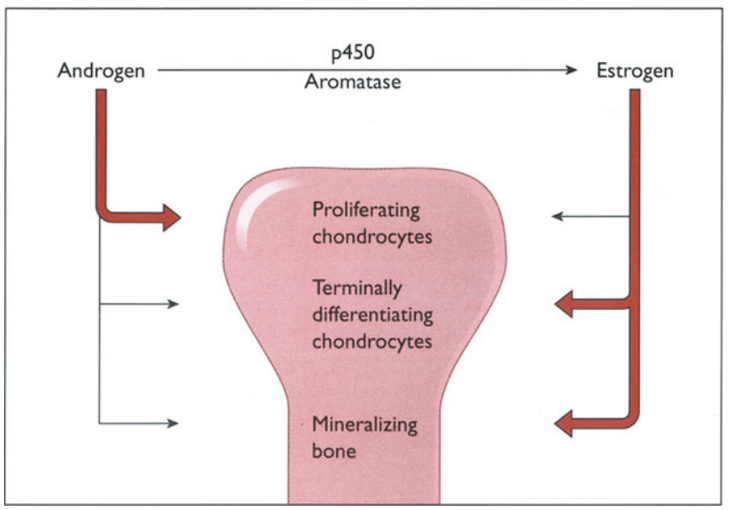



**FIGURE 2-10.** Sex steroids and bone acquisition. Estrogen appears to be essential for normal bone maturation and mineral acquisition in girls and boys. Patients with rare disorders of estrogen resistance or impaired synthesis (aromatase deficiency) have osteopenia and delayed epiphyseal closure [22]. Estrogen therapy results in skeletal maturation and increases bone mineral acquisition [43]. Androgens may also be essential for normal bone mineral accrual and growth, especially for long bones [43a]. Patients with androgen insensitivity syndrome (AIS) have androgen receptor abnormalities that confer partial or complete resistance to androgens. Many of these patients have reduced areal and volumetric bone mineral density after gonadectomy despite estrogen replacement therapy, indicating an essential role for androgens in mineral accrual [43b]. (*Adapted from* Bachrach and Smith [22].)

# Calcium Economics and Bone Health

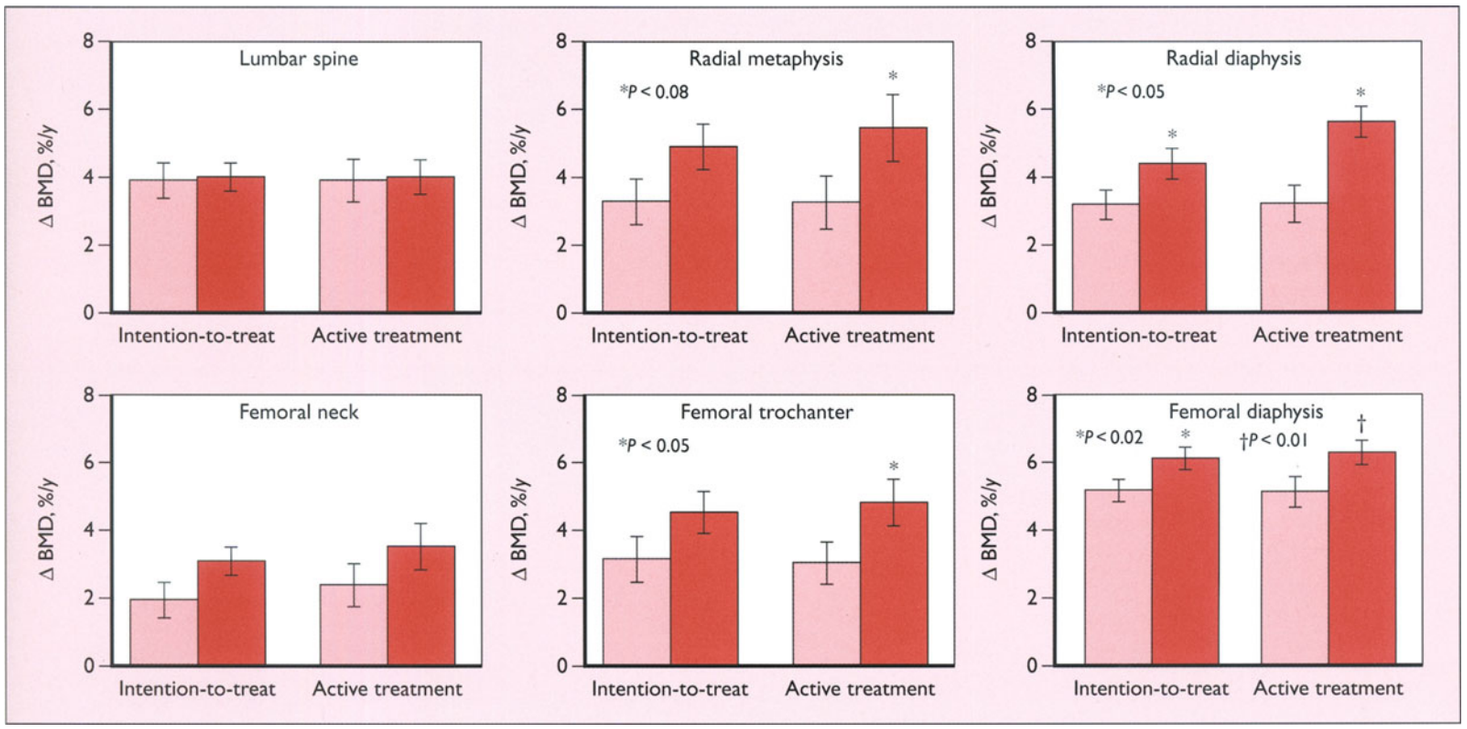



**FIGURE 2-11.** Calcium supplementation and bone accrual. Several controlled trials have shown that increasing calcium intake in childhood and adolescence results in gains in bone mineral density (BMD) [14,15]. In the study results shown, girls who consumed foods supplemented with milk protein gained significantly more bone mineral at the radius, trochanter, and femoral diaphysis than did those in the unsupplemented control group [15]. The greatest gains occurred in girls whose habitual diet contained less than 880 mg/d without supplementation. (*Adapted from* Bonjour *et al.* [15].)

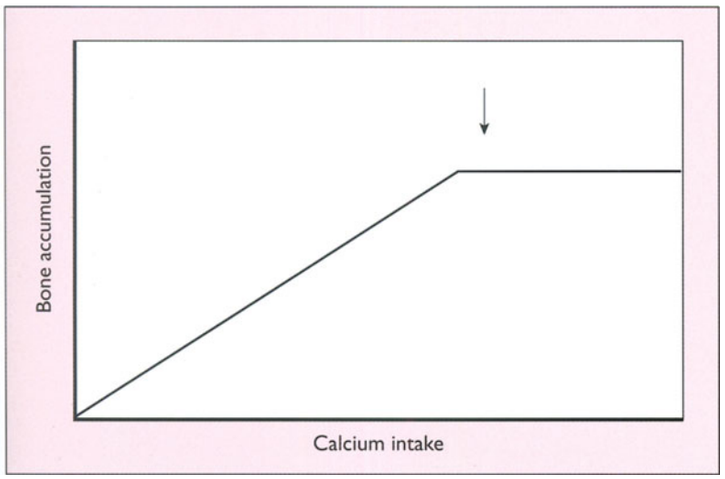



**FIGURE 2-12.** Optimal calcium intake for skeletal health. Calcium retention and bone accrual increase with greater calcium intake until a threshold is reached. Calcium balance studies indicate that calcium retention plateaus at a daily intake of 1200 to 1500 mg/d [44]. Bone mineral acquisition also reaches a maximum at an intake of 1100 to 1200 mg/d, based on calcium supplementation studies (see Fig. 2-11) [14,15].

**DIETARY REFERENCE INTAKE FOR CALCIUM**

| Age, y | Calcium Intake, *mg/d* |
|---|---|
| 1–3 | 500 |
| 4–8 | 800 |
| 9–18 | 1300 |
| 19–50 | 1000 |
| 51+ | 1200 |

**FIGURE 2-13.** Dietary reference intake for calcium. In 1997, the National Academy of Science issued new dietary guidelines for substances related to bone health, including calcium, phosphorus, magnesium, vitamin D, and fluoride. The recommended intake of calcium for each age group is shown. The calcium recommendations for children and adolescents were raised, based on data linking increased calcium with greater bone accrual [16]. Calcium intake of 1300 mg/d is the equivalent of 4.3 glasses of milk.

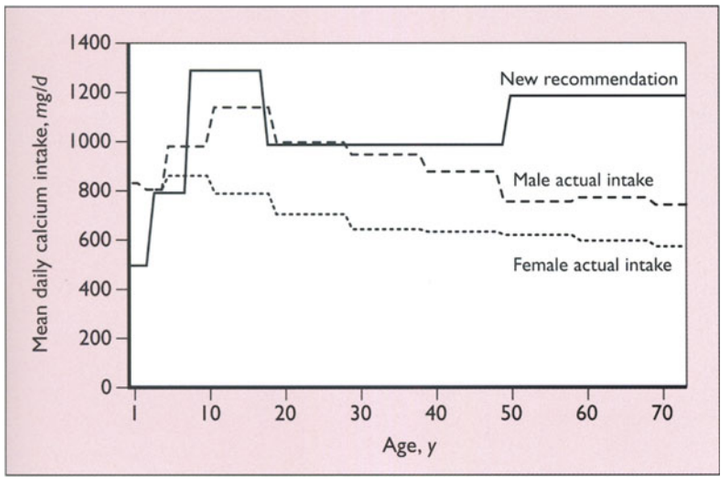



**FIGURE 2-14.** The gap in calcium intake. The mean daily calcium intake falls well below the recommended level, especially during adolescence. Data shown here from the 1994–95 Continuing Survey of Food Intakes by Individuals (CSI) indicate that 86% of girls and 65% of boys aged 12 to 18 years failed to meet the previous recommended daily calcium allowance of 1200 mg/d [28]. The optimal intake for calcium has now been set at 1300 mg/d; thus, the gap between the recommended and the actual intakes of dietary calcium has widened in American youth.

**CALCIUM CONTENT OF COMMON FOODS**

| Foods | Serving Size | Calcium Content, *mg* |
|---|---|---|
| Dairy products | | |
| Milk | 1 cup | 300 |
| Yogurt | 1 cup | 345 |
| Cheese | 1-1/2 oz | 300 |
| Ice cream | 1/2 cup | 100 |
| Frozen yogurt* | 1/2 cup | 60–100 |
| Macaroni and cheese | 1/2 cup | 180 |
| Cheese pizza | 1 slice | 100 |
| Nondairy foods | | |
| Calcium-fortified orange juice | 1 cup | 300 |
| Calcium-fortified cereal* | 1 oz | 160–250 |
| Almonds | 1 oz | 80 |
| Broccoli | 1/2 cup | 35 |
| Soybeans (dry-roasted) | 1/2 cup | 230 |
| Kale | 1 cup | 180 |
| Salmon (canned with bones) | 2 oz | 130 |
| Sardines (canned with bones) | 3-3/4 oz | 380 |
| Tofu (with calcium)* | 1/2 cup | 50–250 |

**Calcium content varies by brand.*

**FIGURE 2-15.** Calcium content of common foods. Meeting the recommended daily intake of calcium is challenging when dairy products are not consumed. Calcium-fortified products offer a means of boosting calcium consumption through nondairy foods.

**BARRIERS TO CALCIUM INTAKE**

| Avoidance of Dairy Products | Limited Intake from Nondairy Sources |
|---|---|
| Substitution of soft drinks for milk | Ethnic dietary preferences |
| Fear of fat | Low calcium content or bioavailability of many foods |
| Lactose intolerance | Paucity of calcium-fortified foods |
| Ethnic dietary preferences | |
| Concerns regarding environmental toxins | |

**FIGURE 2-16.** Barriers to calcium intake. Dairy products provide 75% of the dietary calcium consumed in the American diet. Several factors that contribute to the declining intake of dairy products can be addressed. Low-fat or fat-free milk, yogurt, and cheeses can be substituted for whole-milk products without reducing the calcium content. Furthermore, most lactose-intolerant persons can consume dairy products in small amounts without symptoms. Nondairy sources of calcium, such as breads, cereals, vegetables, and fish, generally have a lower content or less bioavailable form of calcium. Some calcium-rich foods such as tofu, turnip greens, and sardines are not part of the standard American diet.

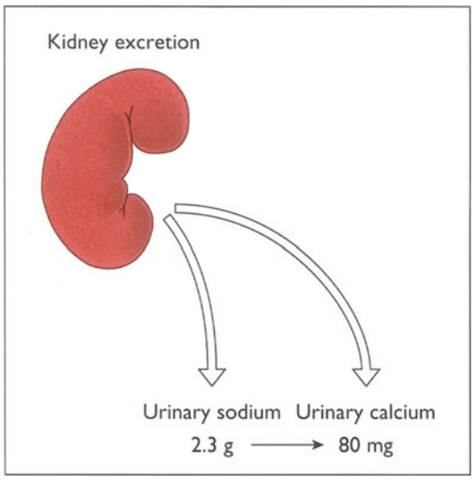



**FIGURE 2-17.** Calcium economics and sodium intake. The net amount of calcium available for bone metabolism reflects the balance of calcium intake, absorption, and excretion. Calcium consumption has declined in recent years, and only 30% to 40% of what is consumed is absorbed [45]. To compound these problems, urinary calcium losses are likely to be on the rise because of increased sodium intake. Calcium and sodium excretion are linked, with 80 mg of calcium lost for every 2.3 g of urinary sodium [46]. Americans are consuming more sodium contained within prepackaged and fast foods. Decreased calcium intake coupled with increased urinary losses may translate to inadequate calcium for optimal bone acquisition.

## Physical Activity and Bone Mass

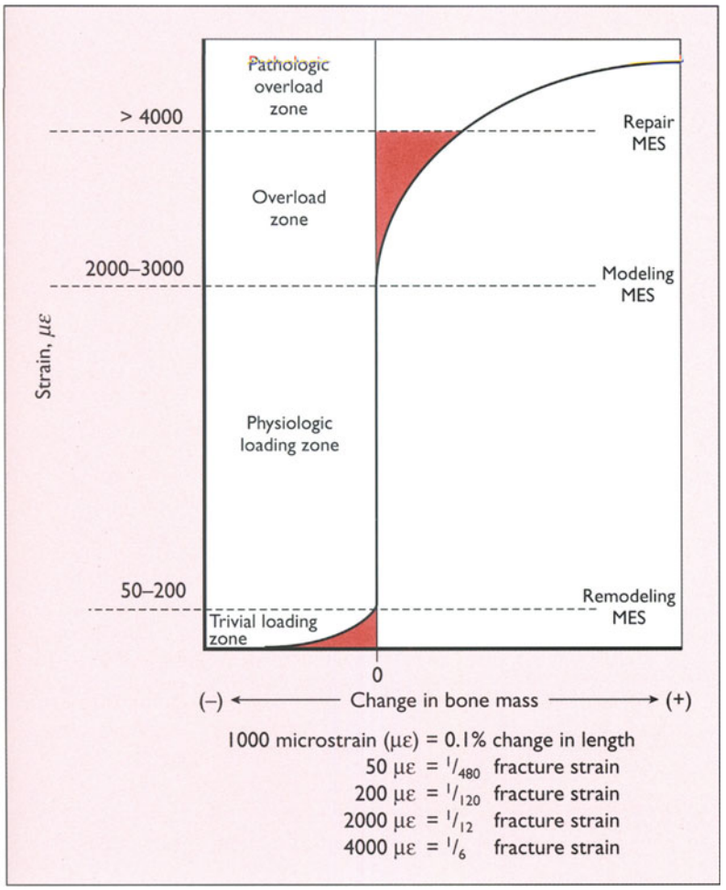



**FIGURE 2-18.** The effects of mechanical loading on bone acquisition. The effect of physical strain on the growing skeleton varies across a range of intensity. According to biomechanical models, when skeletal loading is trivial (as in immobilization), the stimulus for acquisition is insufficient and bone loss occurs. With more moderate (physiologic) loading, neither loss nor gain of bone occurs. In the overload zone, increased strain stimulates bone gain; still greater loading results in formation of poorly constructed bone mineral. MES—minimum effective strain. (*Adapted from* Bailey *et al.* [47].)

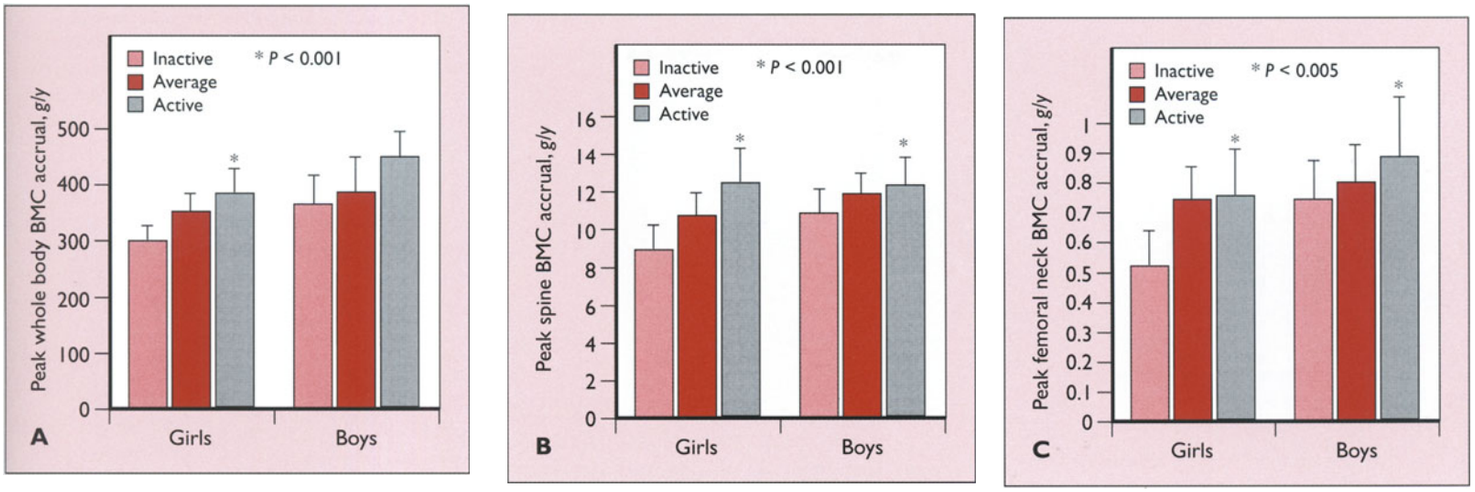



**FIGURE 2-19.** Physical activity is an important stimulus for bone mineral acquisition. Elite childhood athletes can increase bone size and mineral content during childhood and adolescence [17]. However, even everyday activities, such as sports, games, dancing, and physical education classes, can stimulate bone health [3,19]. In a 6-year longitudinal study, Bailey *et al.* [3] found that the most active boys and girls gained significantly more bone mineral content (BMC) in the whole body (**A**), the spine (**B**), and the femoral neck (**C**) during adolescence than did their inactive peers [3]. (*Adapted from* Bailey *et al.* [3].)

**A. JUMPING ACTIVITIES AND BONE MINERAL ACCRUAL IN CHILDREN**

| Study | *N* | Age, y | Sex | Intervention | Results |
|---|---|---|---|---|---|
| McKay [48] | 144 | 6–10 | M,F | Tuck jumps and other activities 3×/wk for 8 mo | Trochanteric BMD increased in intervention group vs control group |
| MacKelvie [49] | 177 | 8–11 | F | 10 min of jumping 3×/wk for 7 mo | Femoral neck and spine BMC and BMD increased in intervention group vs control group in early puberty; no effects of intervention in prepubertal girls |
| Fuchs [50] | 89 | 5–9 | M,F | 100 jumps from boxes 3×/wk for 7 mo | Femoral neck and spine BMC, spine BMD, and femoral neck bone area increased more in intervention group vs control group |

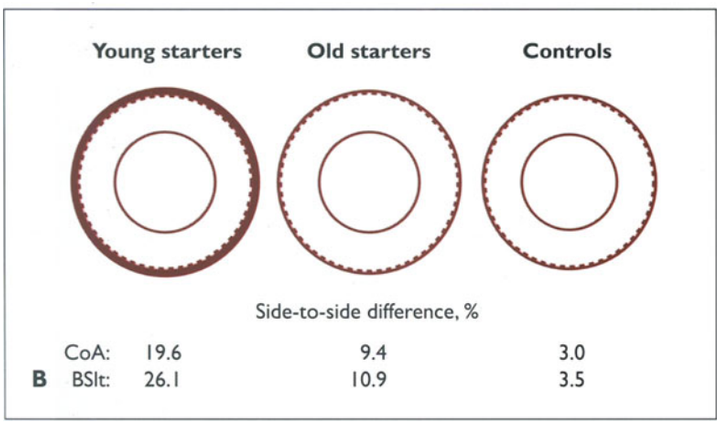



**FIGURE 2-20. A,** Jumping activities increase bone mineral accrual in children. Several controlled trials have shown that brief periods of jumping activity increase bone mass and bone area in prepubertal or peripubertal children. Subjects who jumped for several minutes three times a week gained more bone mass at the hip or spine than those in the control group. If the gains observed in these short-term studies are maintained or increased with ongoing activity, peak bone mass would improve. Introducing jumping activities into the school physical education curriculum may help offset the trend toward inactivity among American youths [29]. BMC—bone mineral content; BMD—bone mineral density.

**B,** Changes in bone structure with physical activity. Long-term loading activities, such as racquet sports, stimulate changes in bone structure as well as gains in bone mineral content. Kontulainen *et al.* [50a] compared differences in bone structure and areal bone mineral density between playing (loaded) and nonplaying arms of 64 female tennis and squash players. Using peripheral quantitative computed tomography (pQCT) to assess bone structure, they found greater side-to-side differences in bone mineral content, cross-sectional area of cortical bone (CoA), total cross-sectional area of bone, cortical wall thickness, and torsional bone strength (BSIt) in racquet players than in age-, height-, and weight-matched control subjects. Athletes who began their sport before menarche (young starters) had greater side-to-side differences than those beginning after menarche (old starters). Differences in these structural bone parameters were greater for the humeral shaft (*shown*) than for distal radius. The dotted line indicates the size of the nonplaying arm, and the *solid line* the circumference of the playing arm. The percent difference between sides is shown by the *shaded area*. The magnitude of side-to-side differences in bone structure (detected by pQCT) was greater than for areal bone mineral density (assessed by dual-energy x-ray absorptiometry). These data confirm the importance of loading activity for building bone strength and mass, particularly during growth. (*From* Kontulainen *et al.* [50a].)

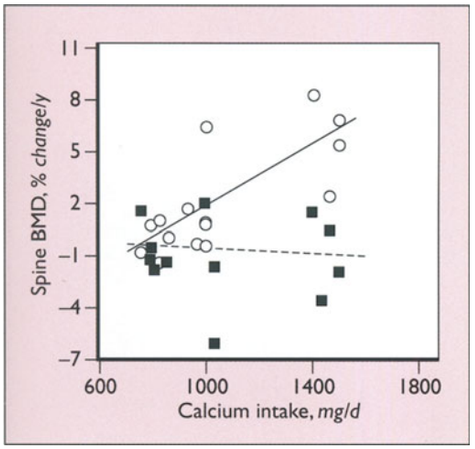



**FIGURE 2-21.** The interaction between calcium and activity. Calcium intake modulates the bone response to physical activity. In a meta-analysis of exercise intervention studies in adults, Specker [20] found that persons in the control group who maintained their usual activity patterns (*closed squares*) experienced no change in bone mass across a range of calcium intakes. Women assigned to the exercise intervention groups (*open circles*) had gains in spinal bone mineral density (BMD) but only if their calcium intake exceeded 1000 mg/d. These studies underscore the important interaction of diet and physical activity in bone health. (*Adapted from* Specker [20].)

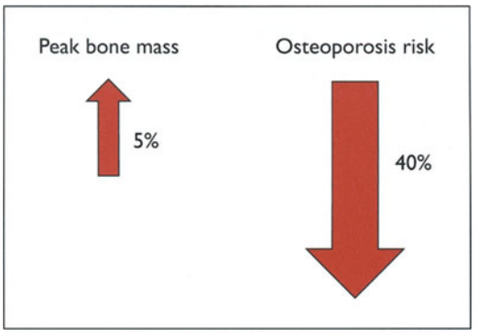



**FIGURE 2-22.** Small differences in peak bone mass mean major differences in skeletal health. The gains in bone mass associated with increasing calcium intake or activity are modest but sufficient to influence skeletal health. A 5% increase in peak bone mass is estimated to reduce the lifetime risk of osteoporosis by 40%. Conversely, the risk of osteoporotic fracture in older adults doubles for each standard deviation (10%) that bone mass falls below the mean value for healthy young adults [51].

**FOSTERING SKELETAL HEALTH**

- Nutrition
  - Avoid high sodium intake
  - Maintain daily calcium intake at recommended level
  - Maintain healthy body weight
- Physical activity
  - Avoid excessive exercise (exercise-associated amenorrhea)
  - Exercise several days a week
  - Perform a variety of weight-bearing activities, including jumping
- Avoid cigarette smoking and alcohol use

**FIGURE 2-23.** Fostering skeletal health. Even the modest gains in bone mass seen in persons with a healthy lifestyle may produce a measurable benefit. Although it may be difficult to convince youths of the relevance of bone health, health care professionals, educators, and the media need to spread the word that osteoporosis prevention begins in childhood.

# Acquired Bone Fragility

**PEDIATRIC DISORDERS ASSOCIATED WITH LOW BONE MASS**

- Anorexia nervosa
- Endocrinopathies
  - Cushing syndrome and iatrogenic glucocorticoid excess
  - Diabetes
  - Growth hormone deficiency
  - Hyperprolactinemia
  - Hyperthyroidism
  - Hypogonadism
- Exercise-associated amenorrhea
- Idiopathic juvenile osteoporosis
- Systemic diseases
  - Asthma
  - Celiac disease
  - Cystic fibrosis
  - Leukemia
  - Post–organ transplantation
  - Rheumatologic disorders

**FIGURE 2-24.** Pediatric disorders associated with bone fragility in childhood. A variety of chronic conditions may threaten bone health during the first two decades of life [23]. In some cases, such as in patients with diabetes or growth hormone deficiency, the deficits may be mild. Osteoporosis and atraumatic fractures have been reported in patients with anorexia nervosa, cystic fibrosis, and glucocorticoid excess, and after organ transplantation. Idiopathic juvenile osteoporosis is a poorly understood syndrome of bone pain and low bone mass that improves spontaneously at puberty.

**COMMON RISK FACTORS FOR POOR SKELETAL HEALTH**

- Nutritional
  - Malabsorption
  - Vitamin D deficiency
  - Calcium deficiency
  - Protein deficiency
  - Calorie deficiency
- Endocrine
  - Sex steroid deficiency
  - Glucocorticoid excess
- Immobility

**FIGURE 2-25.** Common risk factors for poor skeletal health. Myriad pediatric disorders associated with reduced bone mass share common risk factors [23]. Inadequate nutrition, immobility, or endocrine disorders limit gains and increase the loss of bone mineral. Early deficits range in severity from mild reductions in bone mass for age to osteoporosis, a more profound deficit in bone mineral with disruption of bone architecture and vulnerability to pathologic fractures.

**INTERPRETING BONE DENSITOMETRY IN PEDIATRIC PATIENTS**

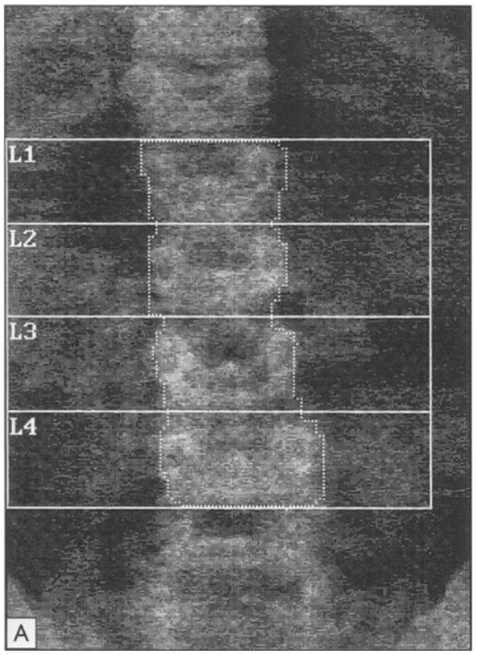
- Normative data are limited
- Need to consider
  - Bone size
  - Pubertal stage
  - Skeletal maturation
  - Ethnicity and race
  - Body composition

**FIGURE 2-26.** Interpreting bone densitometry in pediatric patients. The interpretation of densitometry data in children and adolescents is considerably more challenging than it is in adults. The software provided by most manufacturers of dual-energy x-ray absorptiometry (DXA) equipment may not include pediatric reference data for all skeletal sites. Therefore, clinicians must refer to published norms collected using similar DXA equipment (see Fig. 2-27). Furthermore, bone growth and pubertal stage should be considered when interpreting bone mineral density (BMD) results. Patients with chronic disease often have growth retardation as well as delayed sexual and skeletal maturation, which result in lower BMD values. It may be more appropriate to compare the BMD results from these patients based on bone age or pubertal stage, rather than chronologic age. To correct for smaller bone size, volumetric bone density can be estimated and compared with published values [32,39].

**PEDIATRIC REFERENCE DATA FOR DUAL-ENERGY X-RAY ABSORPTIOMETRY**

| Study | Equipment | Number | Age, y | Sex | Ethnicity | Sites |
|---|---|---|---|---|---|---|
| 52 | Hologic 1000 | 218 | 1–19 | Male, female | Black, white | Spine (L1–4) |
| 53 | Hologic 1000 | 207 | 9–18 | Male, female | White (Switzerland) | Femoral neck, spine (L2–4) |
| 54 | Hologic 2000 Array Mode | >650 | 8–17 | Male, female | Mostly white (Canada) | Femoral neck, whole body, spine (L1–4) |
| 42 | Hologic 1000W Pencil Beam | 423 | 9–25 | Male, female | Asian, black, Hispanic, white | Femoral neck, total hip, whole body, spine (L2–4) |
| 55 | Hologic 2000 | 982 | 5–18 | Male, female | White, black, Hispanic | Whole body |
| 56 | Lunar DPXL/PED | 444 | 4–23 | Male, female | White (Netherlands) | Whole body, spine (L2–4) |

**FIGURE 2-27.** Pediatric reference data for dual-energy x-ray absorptiometry (DXA). Normative pediatric data are now available using a variety of DXA equipment and software. When one uses these data to interpret bone mineral density results, it is important to select reference data collected with the same software and equipment used to study patients, because there are systematic differences in results [57]. Standard deviation scores will vary, depending on the normative data employed. In particular, the percentage of boys defined as having low bone mass is greater when gender-specific data are not employed [58].




**B. BONE MINERAL DENSITY**

| Region | Estimated Area, $cm^2$ | Estimated BMC, g | BMD, $g/cm^2$ |
|---|---|---|---|
| L2 | 8.40 | 3.57 | 0.425 |
| L3 | 9.13 | 4.14 | 0.454 |
| L4 | 9.80 | 5.27 | 0.537 |
| Total | 27.33 | 12.98 | 0.475 |

**FIGURE 2-28. A** and **B,** Low bone mineral density (BMD) in a 15-year-old girl with cystic fibrosis. The patient suffered a first atraumatic fracture of the left forearm at age 9 years. She had been treated with pancreatic enzymes and vitamin D (for malabsorption), calcium supplements, and alternate-day prednisone, for pulmonary disease. Serum calcium, phosphorus, vitamin D, and parathyroid hormone levels were normal. Her spinal BMD determined by dual-energy x-ray absorptiometry was more than 2 standard deviations below normal. Despite increased calcium and caloric supplementation and efforts to wean her off the steroid dose, she continued to lose bone mass. At age 15 years, her spinal BMD was 4.4 standard deviations below normal [42]. BMC—bone mineral content.

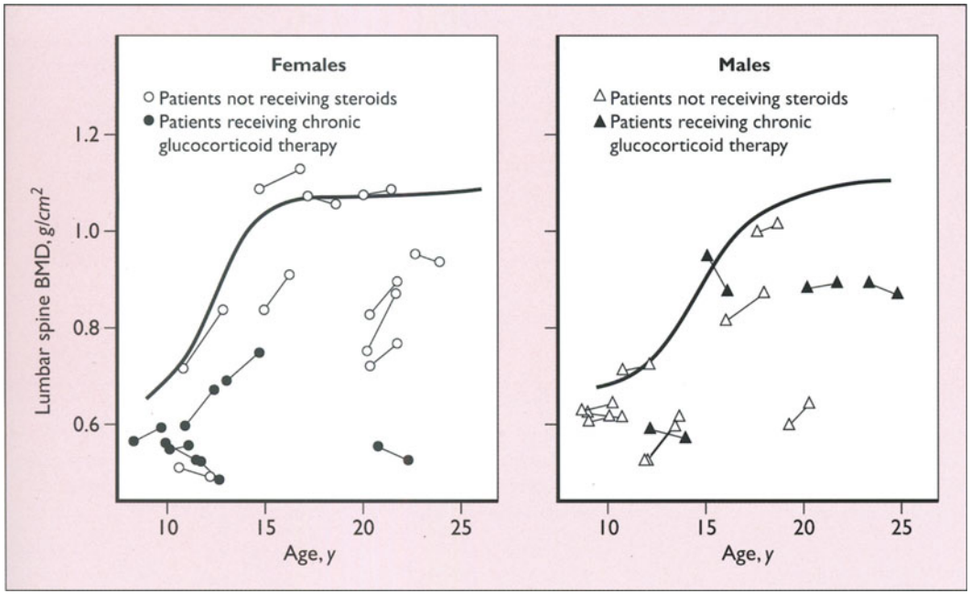



**FIGURE 2-29.** The spectrum of bone mineral density (BMD) in cystic fibrosis. Low bone mass is common in several chronic disorders because of reduced bone acquisition or increased bone loss. Bhudhikanok *et al.* [59] found that spinal BMD was below the mean for age (dark line) in many young patients with cystic fibrosis at study entry. At follow-up 1.5 years later, most patients had gained bone mineral but failed to reach expected values. Bone loss was more common in patients on glucocorticoid therapy. Mean bone mineral values remained low even when corrected for small bone size [59]. (*Adapted from* Bhudhikanok *et al.* [59].)

**DETERMINANTS OF SKELETAL STATUS IN ATHLETES**

- Age at onset of training
- Body mass
- Menstrual status
- Skeletal site
  - Trabecular vs cortical bone
  - Weight-bearing vs non–weight-bearing
- Sport
  - Running
  - Gymnastics
  - Ballet
  - Swimming

**FIGURE 2-30.** Determinants of skeletal status in the athlete. Exercise-associated amenorrhea is another frequent cause of reduced bone mass. The risk of low bone mass in young women who train intensively is dependent on a number of variables. The most profound deficits have been observed as part of the "athletic triad" of disordered eating, amenorrhea, and osteoporosis [60]. Earlier onset of training, low body mass, and delayed or absent menses have been identified as risk factors for low bone mass. Deficits in bone mineral density have been observed at the spine, hip, femoral shaft, and tibia, indicating that weight-bearing activity may not be sufficient to protect against the deleterious effects of hypogonadism [61]. However, the risks to bone health are not equal for all activities. Female gymnasts have greater spinal and hip bone mass (after correcting for bone size) than do runners and nonathletes, despite a high incidence of menstrual dysfunction [62]. By contrast, elite swimmers have no greater bone mass at these sites than do persons in the nonathletic control group [63]. These observations underscore the importance of high-impact activity as a stimulus for bone formation (*see* Fig. 2-18).

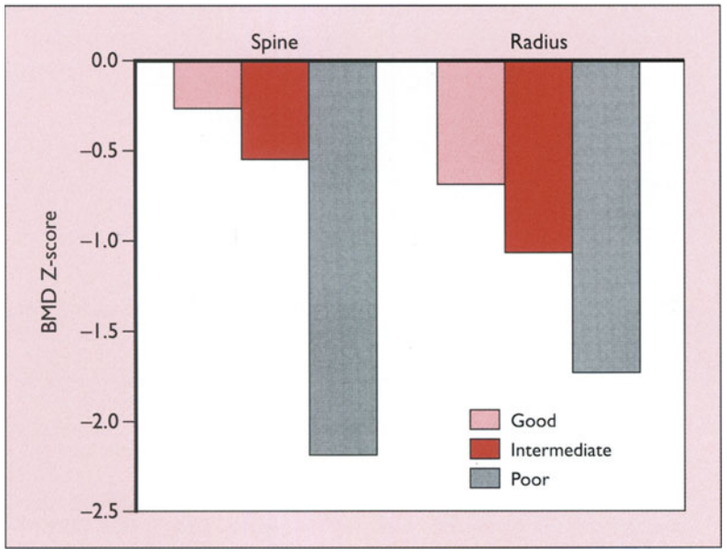



**FIGURE 2-31.** Recovery from osteopenia in anorexia nervosa. Skeletal status after anorexia nervosa in adolescents and young adults is related to the adequacy of recovery from this disorder. Herzog *et al.* [64] examined the bone mineral density (BMD) of 51 women an average of 11.7 years after their first hospitalization for anorexia nervosa. BMD standard deviations (z scores) were significantly related to recovery of weight and menstrual function. However, even those women with a good clinical outcome had persistently low BMD, particularly at the forearm. Low BMD also has been observed in younger persons after recovery from anorexia nervosa, indicating that early deficits in bone mass may not be fully reversible [65,66].

**EVALUATION OF LOW BONE MASS IN CHILDHOOD**

- History
  - Calorie, protein, and calcium intake
  - Activity patterns
  - Fractures
  - Medications
  - Family history of osteoporosis
- Laboratory tests
  - Calcium, phosphorus, creatinine, alkaline phosphatase, blood urea nitrogen
  - 25-hydroxyvitamin D (to assess stores)
  - 1,25-dihydroxyvitamin D (to test conversion to active form)
  - Intact parathyroid hormone
  - Thyroid function
  - Estradiol and testosterone (if adolescent)
  - Genetic studies (optional)
- Bone densitometry

**FIGURE 2-32.** Evaluation of low bone mass in childhood. The cause of poor skeletal health may be apparent from the clinical history, such as chronic glucocorticoid use, anorexia nervosa, and cystic fibrosis. When the cause of low bone mass is unknown, laboratory studies serve to rule out endocrine or renal disorders. The diagnosis of inherited disorders of bone metabolism (such as osteogenesis imperfecta) may be established from DNA analysis of skin biopsies. Bone densitometry is indicated to assess bone mass and to establish a baseline bone mineral density if therapy is initiated. Dual-energy x-ray absorptiometry is currently the preferred method of assessing bone mass in children because of its speed, precision, low radiation exposure, and pediatric reference data.

**THERAPY FOR LOW BONE MASS IN YOUNG PATIENTS**

- Risk-free therapies
  - Address nutritional deficits
    - Increase calorie and protein intake
    - Supplement calcium intake
    - Supplement vitamin D intake
  - Treat endocrinopathies
    - Hyperthyroidism
    - Glucocorticoid excess—endogenous, iatrogenic
    - Diabetes
    - Growth hormone deficiency
  - Avoid immobility
- Possible beneficial therapy
  - Sex steroids
- Experimental therapies
  - Antiresorptive agents
    - Bisphosphonates
    - Calcitonin
  - Anabolic agents
    - Parathyroid hormone
    - Fluoride

**FIGURE 2-33.** Therapy for low bone mass in young patients. Treatment begins by addressing the multiple nutritional and hormonal risk factors. Weight-bearing physical activity should be encouraged, if possible, balancing the risks of slower weight gain or pathologic fracture against the benefits of mechanical loading. For patients requiring glucocorticoid therapy, the minimal effective dose should be used. Sex steroid replacement therapy should be considered for patients with hypogonadism; however, this therapy has not proved sufficient to correct the osteopenia associated with anorexia nervosa [67]. Furthermore, to date, estrogen replacement has not been shown to increase bone mass or to prevent fractures in athletes with amenorrhea in any controlled trial. Antiresorptive agents have not yet been proved safe or effective in children and remain experimental. In theory, anabolic agents such as insulin-like growth factor I or parathyroid hormone may be more promising because low bone density acquired early in life probably reflects a failure to gain bone without or with increased bone loss [59,67]. These agents have not been approved for this purpose in pediatric patients.

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3

# GENETICS OF OSTEOPOROSIS

*Robert F. Klein*

Osteoporosis is one of the most common bone and mineral disorders in all aging communities. It is characterized by low bone mass, and thus low bone strength, which results in fractures from relatively minor trauma. Although osteoporotic fractures are most commonly observed among the elderly, the pathogenesis of osteoporosis starts early in life and involves the interaction of multiple factors [1,2]. Genetic epidemiologic studies provide descriptive data that convincingly demonstrate population and ethnic differences. In addition, studies of familial aggregation and familial transmission patterns and comparisons of twin concordance rates consistently point to susceptibility to developing osteoporosis being inherited in a significant proportion of individuals. The distributions of quantitative skeletal phenotypes in the general population do not conform to a monogenic mode of inheritance. Rather, susceptibility to osteoporosis appears to involve a complex interplay between both genetic and environmental factors. Initial association studies examined polymorphisms in the vitamin D receptor and the impact of dietary calcium and vitamin D intake. Studies on other candidate genes, such as the estrogen receptor or the collagen type I alpha 1 gene, also showed associations that could explain at least part of the genetic background of osteoporosis. Genome-wide linkage studies in humans have revealed a number of chromosomal regions that show probable linkage to bone mineral density, but so far the causative genes remain to be identified. Although the genetic determinants of the common forms of osteoporosis are multiple, recent family studies indicate that it can also occur as the result of mutations in a single gene. Examples are the osteoporosis-pseudoglioma syndrome, caused by inactivating mutations in lipoprotein receptor-related protein 5 gene, and the high bone mass syndrome described in two kindreds thus far, caused by activating mutations of the same gene. Although recent clinical reports show promise, unraveling the very complex genetic basis of skeletal development will be difficult because of the genetic and cultural heterogeneity of the patient populations. A number of laboratories are now using appropriate animal models to pinpoint candidate genes for more focused human investigation. With the steadily increasing body of information evolving from studies on the genetics of osteoporosis, an improved understanding of skeletal biology and metabolic bone disease is emerging. Identification of genes that predispose to osteoporosis will provide numerous opportunities to influence screening, prognosis, and diagnosis, but perhaps the most important application of the discovery of osteoporosis genes will be to the identification of target molecules for new therapeutic approaches.

# Genetic Concepts

**GLOSSARY OF COMMON GENETIC TERMS**

| Term | Definition |
|---|---|
| Allele | One of the alternative forms of the same gene that are present at a given genetic locus |
| Complex disorder | A disorder resulting from the inheritance of more than one genetic locus, environmental factors, and/or genotype-by-environment interactions |
| Genetic map | A diagram of a particular chromosome that depicts the relationship of one genetic locus to another with respect to linear order and distance along the chromosome |
| Genotype | The specific set of alleles inherited by a given individual; it is not uncommon to refer to the genotype of a given individual as the allele present at a particular location along the genome |
| Haplotype | The specific alleles on a chromosome inherited from one parent (haploid genotype); alleles that are physically distant on a chromosome are easily separated during meiosis; thus, a haplotype typically refers to closely grouped loci |
| Linkage | The inheritance of genetic material at two loci that do not assort independently because of their physical proximity on the chromosome |
| Linkage disequilibrium | The nonrandom distribution (*ie*, deviation from the distribution expected from the allele frequencies) of alleles at different loci in haplotypes |
| LOD score | The results of a statistical test to determine whether two genetic loci are linked, which provides the logarithm (to the base 10) of the odds that the two loci are linked |
| Multigenic trait | A phenotype that is influenced by more than one gene |
| Mutation | An alteration in the DNA sequence |
| Phenotype | The biochemical, physiologic, or behavioral profile of an individual based on genetic and environmental factors |
| Pleiotropism | The multiple phenotypic effects of a gene |
| Polygenic trait | A multigenic trait in which each influential gene exerts a small effect |
| Polymorphism | The existence of two or more alleles at a frequency of at least 1% in the population |
| Positional cloning | The cloning of a gene on the basis of its chromosomal location without knowledge of the gene product or function |
| Quantitative trait locus mapping | A strategy used to identify the chromosomal locations of genes in multigenic or polygenic traits |
| Synteny | When two or more genetic loci are present on the same chromosome; when genetic loci are present in a similar chromosomal order between different species (*eg*, humans and mice), the loci are in a region of conserved synteny |

**FIGURE 3-1.** Glossary of common genetic terms. Genetics is the study of inheritance, its patterns and consequences. Over the past three decades, the study of genetic influences has had an impact on every medical discipline. However, the language of genetics remains quite specialized, and certain terms may be unfamiliar. We therefore provide a number of very brief definitions to assist the reader in understanding the information in this chapter.

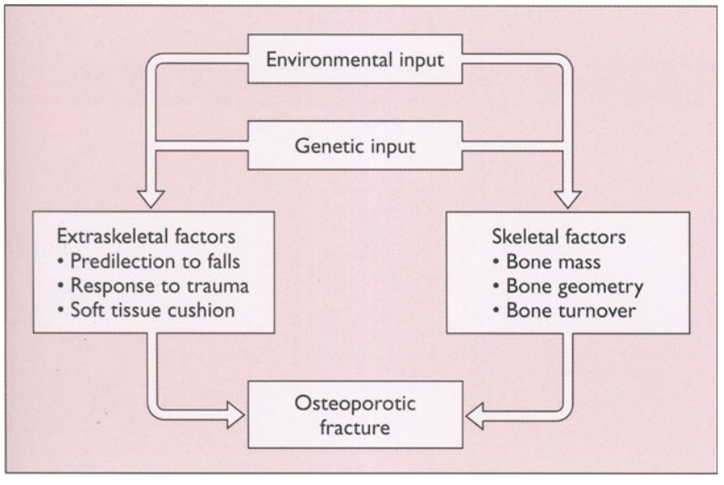



**FIGURE 3-2.** Osteoporosis is a multifactorial disorder. Osteoporosis is a disease characterized by an inadequate amount or faulty structure of bone, or both, resulting in fractures from relatively minor trauma. Fragility fracture is a highly complex event, with extraskeletal risk factors controlling the predilection and response to trauma as well as other factors determining skeletal integrity. Both sets of risk factors have environmental and genetic inputs. Considerable past research has centered on the influence of environmental (nutritional or lifestyle) factors on the occurrence of osteoporotic fracture. With the advent of new molecular genetic approaches, the focus of research has shifted toward genetic factors.

**CHARACTERISTICS OF MULTIFACTORIAL DISORDERS**

| Characteristics | Description |
|---|---|
| Multifactorial influence | Contribution of genetic as well as environmental factors to disease development |
| Phenotypic heterogeneity | Large variety of clinical phenotypes within a syndrome |
| Polygenicity | The effect of many genes that contribute to a disease |
| Genetic heterogeneity | Different genes, or even different alleles of the same gene, may contribute to development of the same phenotype |
| Variable disease onset | The onset of the disease may vary between individuals, onset often late in life |

**FIGURE 3-3.** Characteristics of multifactorial disorders. Like many other common chronic diseases, osteoporosis best fits into the category of mutifactorial genetic disease. This category should be suspected when the pedigree of the disease does not support inheritance in a simple dominant or recessive manner.

The causative factors of multifactorial genetic diseases are composed of both a polygenic component and an environmental component. In the population at large, risk genes are present in low frequency. If any one individual has a particularly large number of risk genes, the latent disorder becomes overt. For another family member to develop the same disease, that individual would have to inherit the same or a very similar combination of genes. The likelihood of such an occurrence is clearly greater in first-degree relatives than in more distant ones. The chances of another relative inheriting the right combination of risk genes also decrease as the number of genes required to express a given trait increases. Elegant and complex mathematical models have been advanced for polygenic-multifactorial disease, but these should not obscure the fact that each of the risk genes must express itself, like any other gene, by way of a specific biochemical product.

## Contribution of Genetics to Skeletal Characteristics

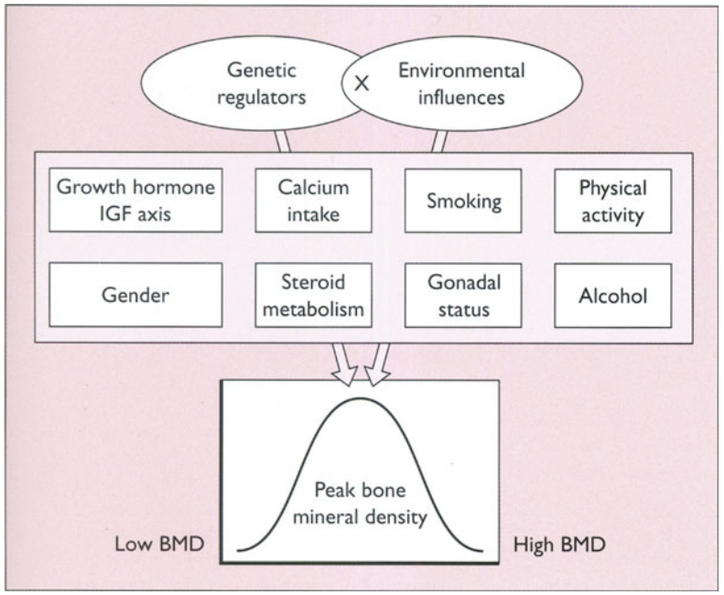



**FIGURE 3-4.** Interaction of genetic and nongenetic factors on peak bone mass. The risk of osteoporosis depends in large degree on the achievement of peak bone mass, which is mostly determined by changes in bone size and volumetric density. These developmental processes are controlled by complex and selective genetic, hormonal, and nutritional and other environmental factors, which tightly interact. There are multiple influences on bone homeostasis as well as a heterogeneity of mechanisms governing skeletal growth; thus, the genetic control of bone mass implicates numerous genes of variable importance during an individual's lifespan. BMD—bone mineral density; IGF—insulin-like growth factor.

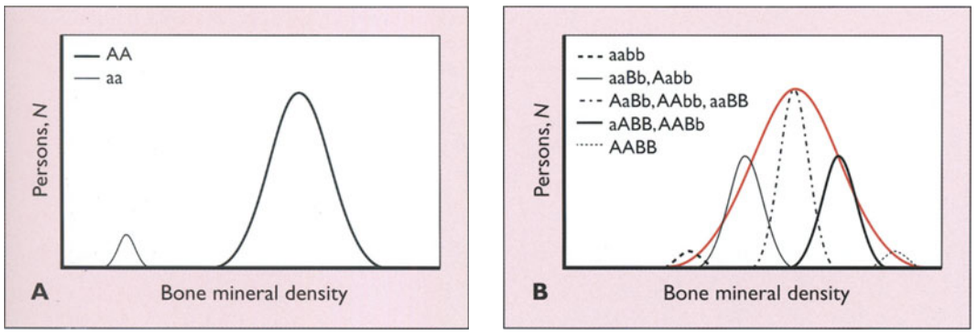



**FIGURE 3-5.** Mendelian versus polygenic determination of bone mineral density (BMD). Mendelian inheritance explains phenotypes that depend on the transmission of alleles at one genetic locus. Polygenic inheritance refers to phenotypes that depend on alleles at multiple genetic loci—aggregates, in a sense, of Mendelian effects. Within biologic populations, continuous traits often fall along a bell-shaped curve that depends on two factors: a mean value and the extent of variation about the mean. The continuous variation in the phenotype is partly attributable to the joint segregation of alleles at multiple genetic loci and by truly continuous environmental variation. By contrast, variation in a Mendelian disorder is discrete and has a single genetic basis. In **A**, the discrete BMD produced by an inactivating mutation at the low-density lipoprotein receptor–related protein 5 (LRP5) locus is contrasted with a hypothetical curve generated by alternative genotypes at two loci. Note that the mutant LRP5 allele that is responsible for the osteoporosis-pseudoglioma syndrome truncates the continuous distribution of BMD, while **B** illustrates the continuous range of BMD that is standard in human populations. For the purpose of this illustration, the normal BMD distribution is produced by five combinations of alleles at two susceptibility loci. In fact, the number of loci that determine BMD are unknown but undoubtedly large.

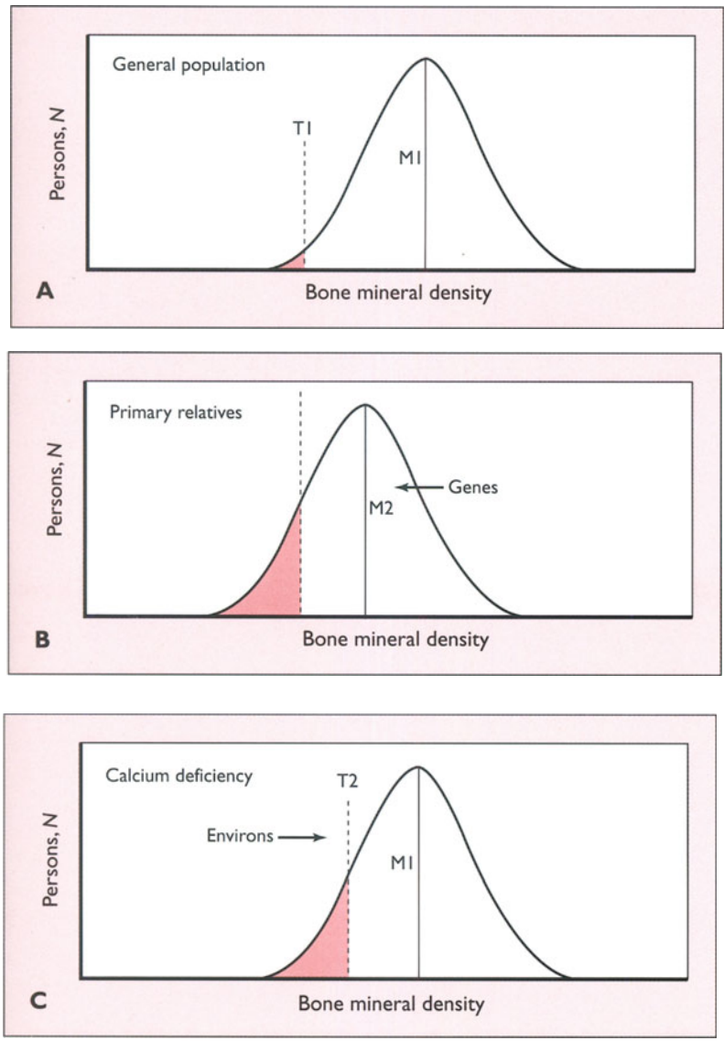



**FIGURE 3-6.** Threshold of susceptibility for osteoporosis. Although most bone strength traits follow a bell-shaped distribution, osteoporotic fractures are either present or absent in individuals. A commonly used explanation for such a relationship is that there is an underlying susceptibility distribution for osteoporosis and fractures in the general population. When bone mineral density (BMD) is used as an example, the individuals who are on the high end of the BMD distribution have little chance of developing osteoporosis (*ie*, they have few alleles or environmental factors that contribute to skeletal fragility). Those who are closer to the low end of the BMD distribution (T1), however, have more of the disease-causing genes and environmental factors and are therefore more likely to experience an osteoporotic fracture. Thus, it is thought that a threshold of susceptibility must be crossed before the disease is expressed. Above the BMD threshold, the individual appears normal; below it, he or she is osteoporotic and at high risk for subsequent fracture. As shown in this figure, both genetics and environment can increase the likelihood of osteoporosis. **A,** Distribution of BMD in the general population. **B,** Distribution of BMD in primary relatives of osteoporosis patients as an example of genetic factors. **C,** Distribution of BMD in calcium-deficient offspring of osteoporotic mothers as an illustration of an environmental factor, which increases the likelihood of falling below the BMD threshold (T2).

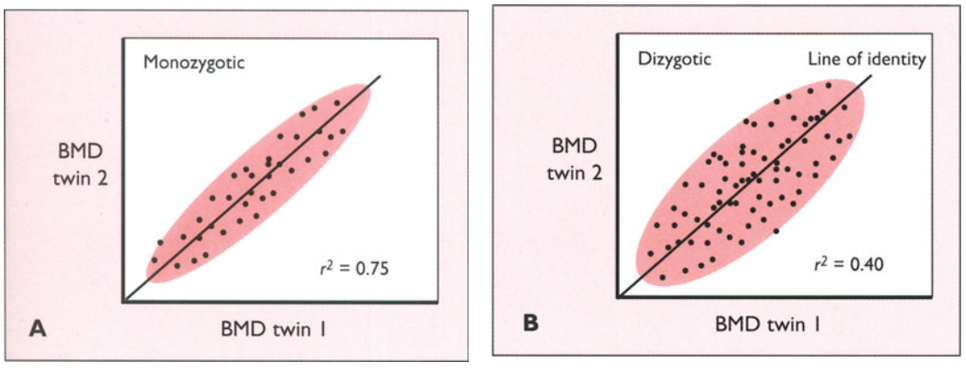



**FIGURE 3-7.** Similarity of bone density in monozygotic (**A**) and dizygotic (**B**) twins. Twin studies have consistently demonstrated a significant genetic contribution to bone mass. Bone density is more similar between monozygotic twins, who are genetically identical, than between dizygotic twins, who share on average half of their genes. Analysis of these data suggests that 75% to 80% of the variance in bone density in individuals matched for age, sex, and general health is genetically determined. However, the consistent evidence across several studies [3–7] of extremely high heritability values may indicate confounding interactions among a relatively small number of genes. BMD—bone mineral density. (*Adapted from* Eisman [8].)

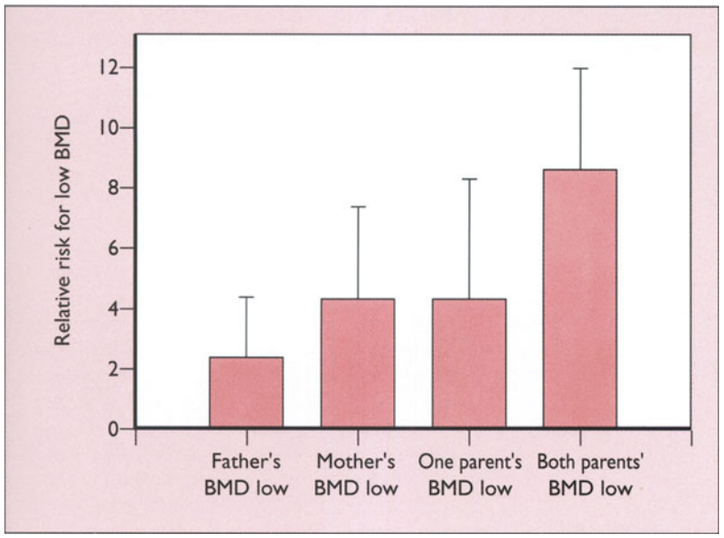



**FIGURE 3-8.** Similarity of bone mineral density (BMD) among members of healthy families. Numerous family studies have demonstrated significant familial correlation for BMD. An early study in a series of mother-daughter pairs estimated the heritability of radial bone mineral content to be 72% [9]. More recently, Jouanny *et al.* [10] found significant correlation between the BMDs of children older than 15 years of age and their parents ($r = 0.27$; $P < 0.0001$). As is depicted here, logistic regression revealed that offspring had a 4.3-fold higher risk of low BMD if one parent had low BMD and an 8.6-fold higher risk when both parents had low BMD.

**HERITABILITY ESTIMATES FOR VARIOUS SKELETAL TRAITS**

| Phenotype | Heritability |
|---|---|
| Lumbar spine BMD | 0.89 |
| Femoral neck BMD | 0.77 |
| Femoral neck axis length | 0.81 |
| Femoral neck width | 0.61 |
| Femoral shaft width | 0.58 |

**FIGURE 3-9.** Heritability estimates for various skeletal traits. Inheritance studies over the past three decades consistently demonstrate a large genetic contribution to many bone phenotypes. Shown here are heritability estimates derived from a large set of sib-pairs [11,12]. Thus far, however, most studies have sampled only women, and not enough studies have examined men to determine whether there are significant gender differences in the heritability of certain skeletal traits [13]. This is an important issue, given the well-described sex differences in the clinical prevalence of osteoporosis and fragility fracture. In this regard, it is significant that studies in laboratory mice have provided evidence of gender-specific genetic influences on both bone density [14] and bone geometry [15]. BMD—bone mineral density.

# Methods in Genetic Investigation

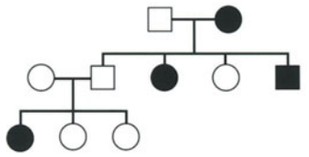
**METHODS FOR DETERMINING HERITABILITY OF COMMON DISEASES**

| Method | Example |
|---|---|
| Twin studies | Higher incidence in monozygotic than in dizygotic twins |
| Familial aggregation | Higher incidence in relatives of affected patients |
| Ethnic differences | Higher incidence in certain ethnic groups |
| Adoption studies | Higher incidence in biologic than in adoptive parents |
| Presence in Mendelian disorders | Mendelian disorders with osteoporosis as one component |

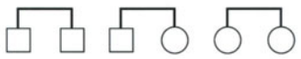
**FIGURE 3-10.** Methods for determining heritability of common diseases. Although it is not possible to assess the likelihood that an individual will develop a particular disorder, it is possible to estimate what proportion of cases result from genetic factors, as opposed to environmental factors. This is referred to as heritability, which can be defined as the proportion of the total phenotypic variance of a condition that is caused by additive genetic variance. Heritability is expressed either as a proportion of 1 or as a percentage.

Estimates of the heritability of a condition or trait provide an indication of the relative importance of genetic factors in its causation; so the greater the value for the heritability, the greater the role of genetic factors. The best studies of heritability ascertain all patients and relatives with a disease, then evaluate concordance as a function of relationship. Twin studies are the most powerful method of estimating heritability. Concordance in identical (monozygotic) twins is weighed against the concordance in fraternal (dizygotic) twins to produce an estimate of heritability. Although very powerful, twin studies are susceptible to bias. Other methods of evaluating heritability include ethnic differences and familial aggregation of disease, but these are weaker methods than twin studies because environmental factors may differ among ethnic groups and increasingly mobile families.

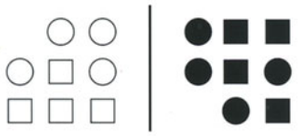
**Linkage analysis**
Look for co-inheritance of phenotype and/or genotype in related populations. This can be carried out with a series of polymorphic genetic markers. It is less suitable for the study of complex diseases, such as osteoporosis where multigeneration families are difficult to come by and the mode of inheritance for the disease is unclear.



**Allele sharing in sib-pairs**
Look for co-inheritance of phenotype and/or genotype in siblings. This approach does not involve constructing a model of disease inheritance and, because of this, has been widely used in genetic mapping of complex diseases.



**Candidate gene studies**
Look for association of a marker allele with disease by comparison of its frequency in affected individuals with unaffected individuals. A potential pitfall with such studies is that they can give spurious results due to population stratification, particularly when the sample sizes are small and when insufficient care has been paid to matching cases and controls.



**Transmission disequilibrium testing**
Trios of parents and affected individuals are genotyped at a polymorphism in or near the candidate gene. Alleles transmitted from the parents to the affected offspring are the "affected" sample and the alleles not transmitted from the parents are used as "control" alleles. This within-family design eliminates spurious association results due to population stratification.

**Experimental crosses in animals**
Set up experimental crosses of animals using one strain that shows increased susceptibility to the disease under study and another that does not (for example, high and low bone mass). Linkage studies and allele sharing studies can then be performed in the large number of progeny that result from the breeding program.

**FIGURE 3-11.** The main strategies for identification and characterization of genes involved in the pathogenesis of osteoporosis. All these approaches search for an association between a relevant skeletal trait (bone mineral density [BMD], hip axis length, bone remodeling marker, fracture), and a series of polymorphic genetic markers. Genetic studies involve typing a large number of markers distributed at regular intervals across the genome (a whole genome search), or typing markers that are concentrated near genes of interest (candidate genes). Candidate gene approaches have been widely used in the search for osteoporosis susceptibility genes (see Figure 3-17). While candidate gene studies are generally more practical than linkage analyses in confirming an osteoporosis gene, they are also prone to giving false-positive results. Consequently, candidate gene associations should be regarded as provisional, pending replication in other populations or confirmation by techniques that use family-based controls, such as the transmission equilibrium test. Regions of chromosomes that contain alleles that influence a continuous trait (*eg*, BMD) are termed *quantitative trait loci* (QTL). The genetic tools most commonly used for QTL identification are whole genome scans in multigenerational families, multiple sib-pairs, and large populations of genetically heterogeneous mice. (*Adapted from* Stewart and Ralston [16].)

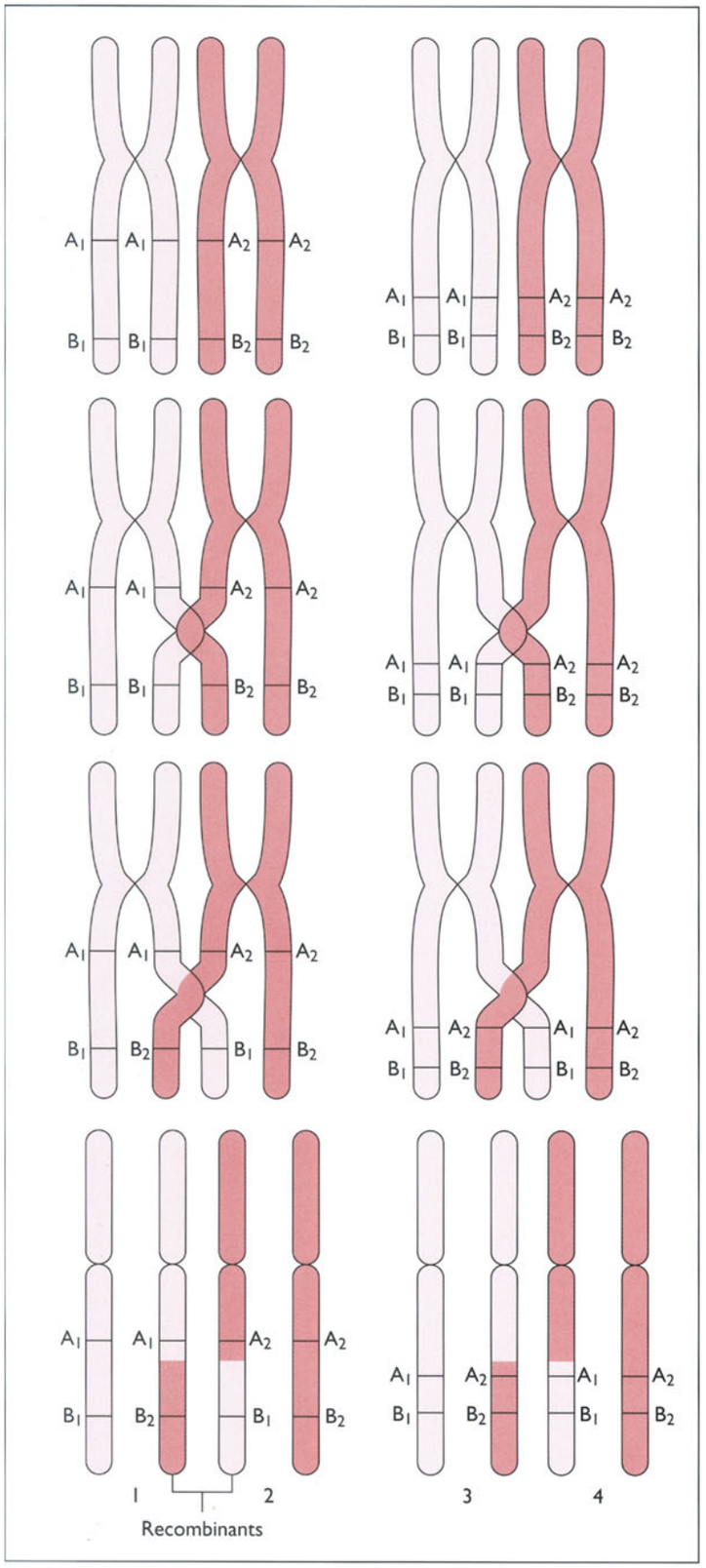



**FIGURE 3-12.** Principles of genetic linkage. Genetic linkage refers to the fact that genes are physically attached to one another along the length of the chromosome. Consequently, two genes that are close together on a chromosome are usually transmitted together, unless a recombination event separates them. Recombination, which occurs during meiosis, is useful for mapping genes, because it provides a landmark that delineates borders for the location of a gene. The odds of a crossover, or recombination event, are proportionate to the distance that separates them. Thus, genes that are far apart (**1** and **2**) are more likely to be separated by a recombination event than genes that are close together (**3** and **4**). Given large pedigrees or populations, these features make it possible to calculate the genetic distance between two genes. Distances between genes on a chromosome can be quantified by their physical distance from each other in millions of base pairs (megabases) or by their genetic distance, as measured by the frequency of recombination between the two genes per generation. The genetic distance between two loci is measured in centiMorgans (cM), in honor of T.H. Morgan, who first discovered the process of crossing over in 1910. One cM is equal to a recombination frequency of 1% and, on average, covers approximately one megabase of DNA. However, the relationship between linear and genetic distance is not absolute. The frequency of recombination, and thus the genetic distance between genes in specific regions of the genome, may differ, depending on the sequence itself or the ancillary proteins that cover the DNA.

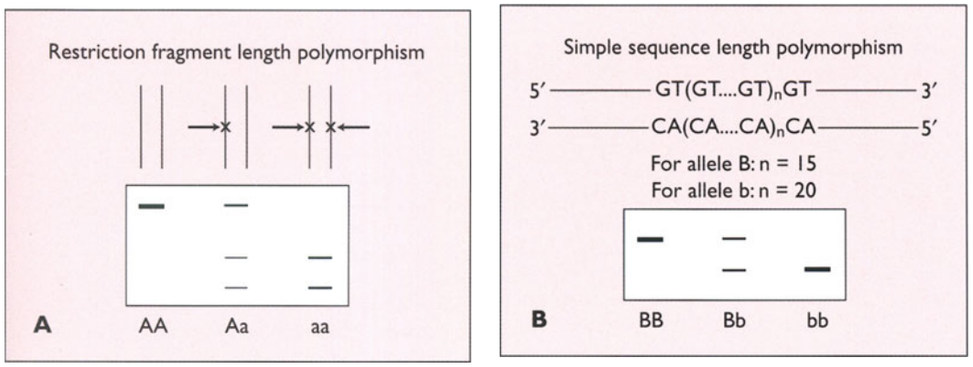



**FIGURE 3-13.** Common marker genotyping assays. To identify an osteoporosis gene, its influence on a skeletal trait must be detected amid considerable "noise" from other quantitative trait loci and nongenetic sources of variation. To accomplish this, laboratory techniques have been developed to detect polymorphisms of loci distributed throughout the genome. Such genetic variation provides a means of distinguishing the maternal and paternal chromosomes in an individual, as well as providing markers of different regions along the chromosomes. This approach has greatly facilitated the analysis of large populations of subjects, making it possible to trace inheritance, and opened the door to genetic analysis of quantitative traits that have previously been resistant to analysis. Two of the more commonly used methods of identifying allelic differences are illustrated here. Each of these methods exploits differences in DNA sequences (alleles) that are easily detected on standard agarose or denaturing polyacrylamide gels. **A,** Schematic electrophoretic pattern for restriction fragment length polymorphisms. Each pair of parallel lines represents a DNA segment. The three possible genotypes are inferred from the electrophoretic pattern; A— absence of the restriction site; a— presence of the restriction site. More recent mapping efforts have utilized primarily microsatellite markers, also known as simple sequence length polymorphisms (SSLPs), which are naturally occurring variations in the number of repetitive base pair sequences. SSLPs are readily genotyped by polymerase chain reaction (PCR) amplification using oligodeoxynucleotide primer pairs specific to each marker. **B,** Schematic electrophoretic pattern for SSLPs. Unique DNA sequences, depicted as lines, flank a tract of (GT/AC)n repeats. The number of repeat units, *n*, varies with genotype, as indicated. (*Adapted from* Blank [17].)

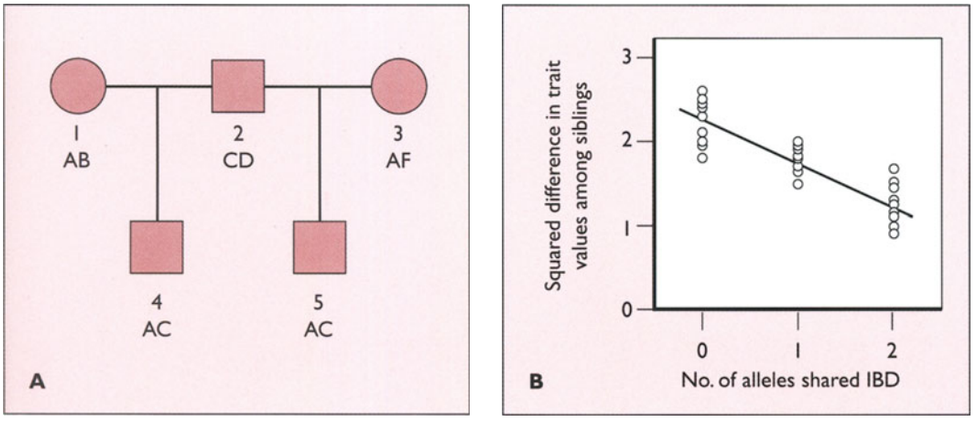



**FIGURE 3-14.** Sib-pair allele-sharing methods. Nonparametric techniques have become popular for localizing genes that confer increased susceptibility to complex diseases because they do not rely on precise specification of an inheritance model. The objective of allele-sharing methods is to determine whether related individuals affected with a given disease or phenotype inherit copies of particular genomic regions identical by descent (IBD) more often than would be expected by chance under independent segregation. These experiments are based on the premise that siblings exhibiting similar values for a quantitative trait would be more likely to share a common chromosomal region near a quantitative trait locus influencing that trait. Studies examining affected sibling pairs often do not include parents; therefore, only *identity by state* (IBS) information is available. It cannot be determined with certainty whether siblings share alleles that are descended from the same allele in an ancestral generation (IBD) or whether the alleles are coincidentally the same size and hence inferred to be identical (IBS). If many siblings are available, however, it may be possible to infer IBD status without parental genotype. IBD allele sharing provides information about linkage, while IBS allele sharing provides information about population level association between the marker and the trait of interest. As is shown in **A**, individuals 4 and 5, who are half-siblings, share the C allele IBD because both inherited it from a common ancestor, their father. Alternatively, while both of them have an A allele, these alleles are not IBD but, rather, IBS because they were inherited from the unrelated mothers of the two half-siblings and cannot be traced back to a common ancestor. In addition, while individuals 1 and 3 cannot share any alleles IBD, as they are unrelated, they share the A allele IBS. Sibling pair linkage analysis for quantitative traits involves linear regression of the (squared) difference in trait values within sibling pairs (the dependent variable) on the number or proportion of alleles shared IBD (the independent variable). If a particular trait is influenced by genetic factors, individuals who are more similar with respect to a given trait—those exhibiting a smaller squared difference—are expected to share a greater number of alleles IBD at marker loci close to a gene influencing the trait of interest. A regression coefficient greater than or equal to zero suggests that the genetic marker does not occur close to a gene influencing the trait, but a significant negative regression coefficient (as shown in **B**) indicates linkage between the marker and a trait-influencing gene.

# Genes and Metabolic Bone Disease

**MONOGENIC BONE DISEASE GENES**

| Disease | OMIM No. | Gene | Genomic Locus |
|---|---|---|---|
| Pyknodysostosis | 601105 | CTSK | 1q21 |
| Camurati-Engelmann disease | 131300 | TGFβ1 | 9q13 |
| Osteopetrosis, autosomal recessive | 604592 | TCIRG1 | 11q12 |
| Osteoporosis-pseudoglioma/high bone mass | 259770 | LRP5 | 11q12 |
| Osteopetrosis, autosomal dominant | 602727 | CLCN5 | 16p13 |
| Sclerosteosis/van Buchem's disease | 605740 | SOST | 17q12 |
| Osteogenesis imperfecta | 120150 | COL1A1 | 17q22 |
| Paget's disease/familial expansile osteolysis | 603499 | TNFRSF11A | 18q21 |

**FIGURE 3-15.** Monogenic bone disease genes. Using linkage analysis in extended families, considerable progress has been made in initially identifying chromosomal loci and then eventually the causative genes for a number of rare monogenic bone diseases. Some of these monogenic disease genes may contribute to regulation of bone mineral density in the normal population. For example, polymorphisms in the transforming growth factor beta 1 (TGFβ1) gene have been associated with osteoporosis in population studies [18,19].

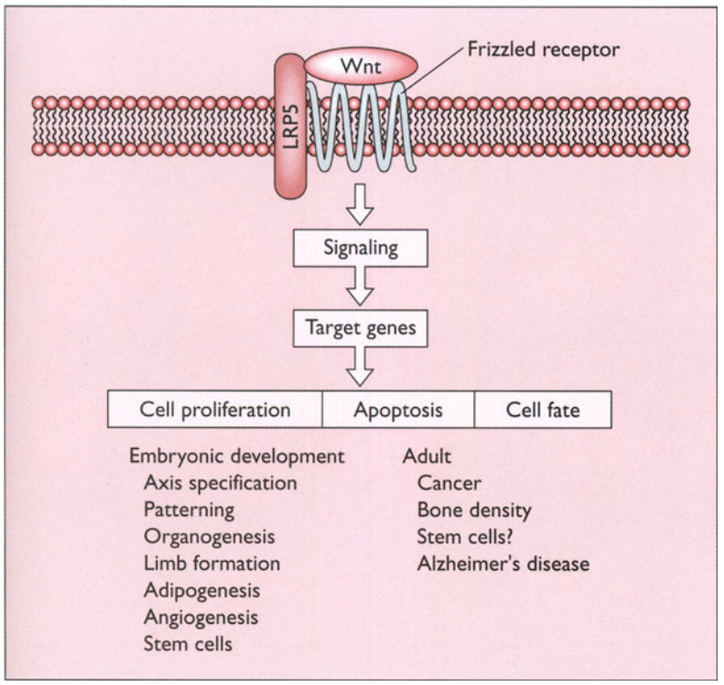
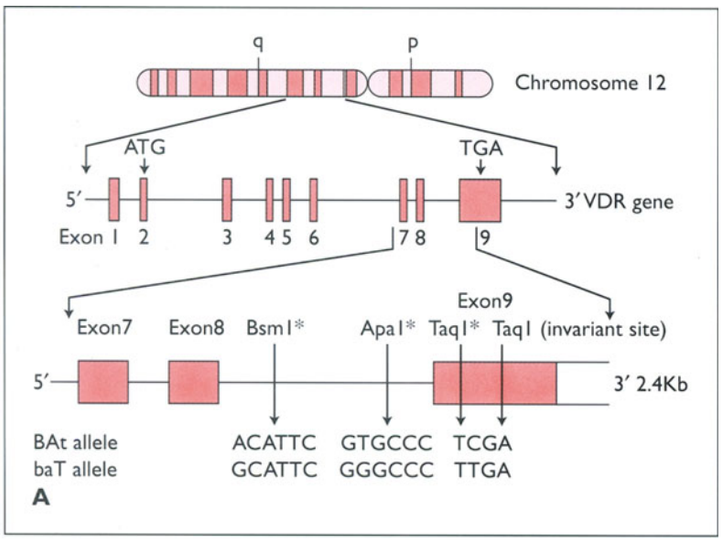



**FIGURE 3-16.** LDL receptor-related protein 5 (LRP5) and peak bone mass. One approach to identifying genes for bone density is through families segregating apparently Mendelian forms of abnormal bone density. In human pedigrees, significant linkage to the centromeric portion of chromosome 11 (11q12-13) has been observed in two different clinical settings. The first is the autosomal recessive osteoporosis-pseudoglioma syndrome (OPS) [20,21], and the second is an autosomal dominant trait characterized by high bone mass [22,23]. Recent studies have succeeded in identifying the genetic origin of these two syndromes. They are allelic disorders resulting from different mutations of the same gene, LRP5. OPS patients harbor inactivating mutations in LRP5, while an activating mutation (Gly171Val) in LRP5 is responsible for the high bone mass syndrome. LRP5 is involved in the Wnt canonical signaling pathway. Secreted Wnts are thought to interact with serpentine transmembrane receptors of the frizzled gene family and co-receptors such as LRP5. Members of the Wnt family of secreted signaling molecules have been implicated in regulating chondrocyte differentiation and skeletal morphogenesis. Beyond this, the role of LRP5 in the determination of bone mass is unclear. However, these results highlight a new pathway that is likely to play a role in the attainment of peak bone mass and, therefore, could be an important pathway for understanding more common forms of osteoporosis.

**CANDIDATE GENE POLYMORPHISMS IMPLICATED IN THE PATHOGENESIS OF OSTEOPOROSIS**

| Category | Candidate Gene | Location |
|---|---|---|
| Bone matrix proteins | Collagen type I alpha 1 | 17q22 |
| | Collagen type I alpha 2 | 7q22 |
| | Osteocalcin | 1q25 |
| | Matrix Gla protein | 12p12 |
| | Collagenase | 11q22.2 |
| | Alpha HS2 glycoprotein | 3q27 |
| Cytokines and growth factors | Interleukin-1 | 2q13 |
| | Interleukin-6 | 7p21 |
| | Insulin-like growth factor I | 12q23.2 |
| | Transforming growth factor beta | 19q13 |
| Calciotropic hormones and receptors | Vitamin D receptor | 12q13 |
| | Estrogen receptor | 6q25.1 |
| | Androgen receptor | Xq12 |
| | Parathyroid hormone | 11p15 |
| | Parathyroid hormone receptor, type 1 | 3p22 |
| | Calcitonin receptor | 7q21.3 |
| | Calcium-sensing receptor | 3q21-24 |
| Miscellaneous | Aromatase | 15q21.1 |
| | Apolipoprotein E | 19q13 |
| | Methylenetetrahydrofolate reductase | 1p36.3 |
| | Peroxisome proliferator-activated receptor gamma | 3p25.2 |

**FIGURE 3-17.** Candidate gene polymorphisms implicated in the pathogenesis of osteoporosis. Numerous experimental approaches can be employed to identify genetic loci that contribute to the risk of osteoporosis. One of the most commonly employed experimental designs is that of candidate gene analysis, which seeks to test the association between a particular genetic variant (*ie*, allele) and a specific trait. Many of these candidate gene studies use population-based association methods. As applied to the study of osteoporosis, two samples are collected: a group of osteoporotic patients and a control group of nonosteoporotic subjects. The allele frequencies at a polymorphism within or near the candidate gene are then compared between the two groups. Evidence of differences in allele frequencies within the two populations (association) may be the result of linkage disequilibrium with the candidate gene or possibly with another gene in close proximity; however, in practice, the candidate gene is thought likely to be the cause of the disease. Unfortunately, it is well recognized that admixture, heterogeneity, or stratification of a population may result in significant association, even when there is no susceptibility locus in the chromosomal region [24]. Therefore, the results of the population-based association tests are often suspect and difficult to interpret. Despite the known limitations of the population-based association study, it is a commonly used experimental design.



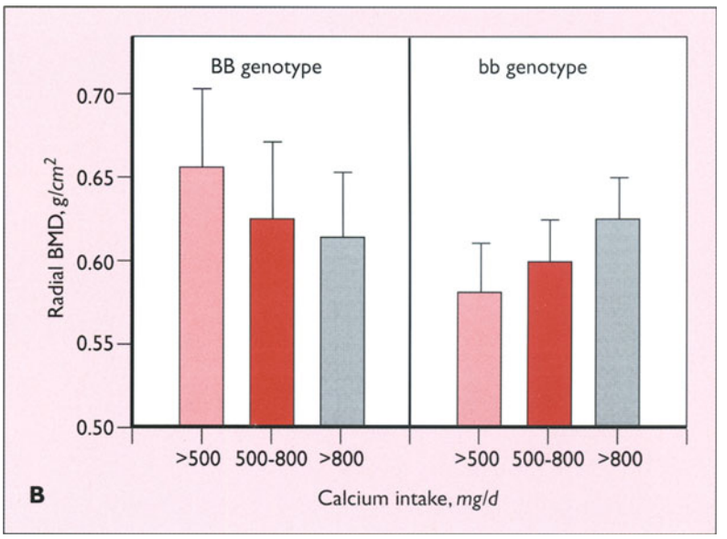




**FIGURE 3-18.** Association between vitamin D receptor gene alleles and bone mineral density (BMD). Among the several candidate osteoporosis genes, the gene encoding the vitamin D receptor (VDR) was the first to be proposed as a major locus for the genetic effect on bone mass. Morrison *et al.* [25] identified three common polymorphisms in the 3′ region of the VDR gene that were recognized by the restriction enzymes *BsmI*, *ApaI*, and *TaqI* (**A**). These were found to be associated with BMD in the Australian population [25]. However, the results of subsequent association studies in other populations have been conflicting, and a meta-analysis incorporating the results from 16 studies concluded that the VDR genotype was associated with only modest effects on BMD [26]. Of some interest, calcium balance experiments in patients with different VDR-*BsmI* genotypes indicate an influence on intestinal calcium absorption [27]. Furthermore, in the setting of calcium deficiency, the *bb* genotype is associated with low BMD [28], compared with the other genotypes (**B**). In calcium deficiency, patients with the *bb* genotype may therefore be especially sensitive to calcium deprivation. Failure to take into account dietary calcium (or for that matter other yet to be discovered confounding factors) in prior population studies may have limited their ability to detect significant associations. More recently, a new polymorphism detectable by the restriction enzyme *FokI* in exon 2 of the VDR gene has been identified. This polymorphism results in a three–amino acid difference in VDR length between *FF* and *ff* individuals, and in vitro studies found that transcriptional activation was higher with the short form (*FF*) of the VDR gene [29]. A number of association studies in populations from around the world have shown that postmenopausal women with the *ff* genotype have lower BMD than those women with the *FF* genotype [30–32]. In contrast with these association studies, two large sib-pair studies failed to find evidence of linkage with the VDR locus at 12q13 [11,33]. (*Adapted from* Kelly [34].)

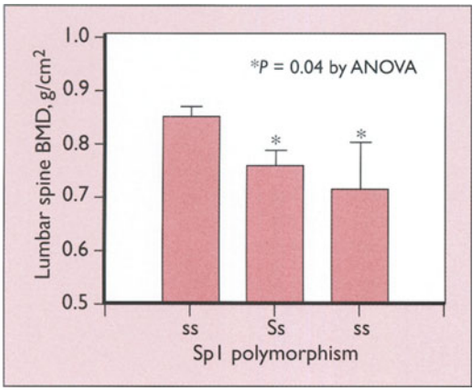



**FIGURE 3-19.** Association between type I collagen gene alleles and bone mineral density (BMD). Type I collagen is the major structural protein of bone. Abnormalities in type I collagen have been shown to result in osteogenesis imperfecta, and mutations in the COL1A1 and COL1A2 genes, which encode the type I collagen proteins, have been well documented in patients with osteogenesis imperfecta. As a result, more subtle polymorphisms in the COL1A1 and COL1A2 were hypothesized to account, in part, for the genetic determination of BMD [35]. Some studies of the regulatory region of COL1A1 have supported an association with bone mass [36,37]. In the study of postmenopausal British women shown here, a common polymorphism was identified that results in a G to T substitution at the first base of a consensus site for the transcription factor Sp1 in the first intron of COL1A1 [36]. Lumbar spine BMD values were significantly higher in women homozygous for the wild-type allele (genotype termed *SS*) compared with women who were heterozygous (Ss genotype). Moreover, the unfavorable *Ss* and *ss* genotypes were overrepresented in patients with severe osteoporosis and vertebral fractures (54%), compared with controls (27%), equivalent to a relative risk of 3 (95% confidence interval, 1.6–9.6). The mechanism by which the Sp1 polymorphism predisposes to osteoporosis is yet to be fully defined, but preliminary data have shown evidence of differences in allele-specific transcription and collagen protein production [38].

**QTL ASSOCIATED WITH BONE DENSITY OR SIZE**

| Genetic Analysis | Phenotype | QTL | Reference |
|---|---|---|---|
| Linkage | Low BMD | 1p36 | [39] |
| | | 2p23-34 | |
| | | 4qter | |
| Sib-pairs | Forearm BMD | 2p | [40] |
| | | 13q | |
| Sib-pairs | Lumbar or femoral BMD | 1q21-33 | [11] |
| | | 5q33-35 | |
| | | 6p11-12 | |
| Linkage | Lumbar or femoral BMD | 4q32.1 | [41] |
| | | 10q26.3 | |
| | | 12q24.3 | |
| Sib-pairs | Femoral neck axis length | 5q11-12 | [12] |
| | | 4q11-12 | |

**FIGURE 3-20.** Quantitative trait loci (QTL) associated with bone density or size. To date, traditional linkage analysis has been successfully employed to discover major contributory genes in monogenic disorders (see Figure 3-15), but this mapping approach has limited ability to detect genes with more modest effects. In the latter case, different approaches, such as nonparametric allele-sharing methods (*ie*, affected sib-pair analyses, transmission/disequilibrium testing), are considerably more powerful. In this respect, recent studies have revealed a number of chromosomal regions (QTL) containing genes that appear to regulate bone density or femoral bone geometry. A major goal of current research is the identification of the particular osteoporosis gene or genes residing within each of these QTL.

**QTL FOR BMD IN INBRED STRAINS OF MICE**

| Chromosome | Map Position, *Mb* | Human Syntenic Region | Reference |
|---|---|---|---|
| 1 | 170 | 1q23* | [42–44] |
| 2 | 19 | 10p15-13/9q33-34 | [45] |
| 2 | 81 | 2qter | [42] |
| 4 | 122 | 1p36* | [42,44] |
| 5 | 76 | 4p12-4q21 | [43] |
| 6 | 117 | 3p26-25/12p12-13 | [44] |
| 7 | 19 | 19q13 | [42,45] |
| 7 | 115 | 10q25-26* | [44] |
| 9 | 87 | 6q14-15 | [44] |
| 11 | 64 | 17p13 | [42,44,46] |
| 11 | 90 | 17q22 | [45] |
| 13 | 21 | 5q31-35* | [43,46] |
| 13 | 56 | 1q41-43/7p14-13 | [44] |
| 14 | 64 | 13q14-21* | [44] |
| 15 | 75 | 8q24/22q13 | [43] |
| 18 | 47 | 5q23-31 | [44] |

**FIGURE 3-21.** Quantitative trait loci (QTL) for bone mineral density (BMD) in inbred strains of mice. In searching for osteoporosis susceptibility genes, animal studies are essential. For a number of reasons, the laboratory mouse has proved to be an especially powerful tool for the identification and mapping of skeletal QTL. First, there is a wide range of bone phenotypic variation in genetically characterized animals, which is a prerequisite for QTL analysis. Second, factors such as short generation interval, ability to make designed matings and raise very large populations relatively inexpensively, and capacity to control or experimentally alter environmental factors enable QTL experiments in mice to have increased power, precision, and flexibility. And third, the mouse is an anchor species in comparative genome maps representing homology among mammalian species. It has been estimated that 80% of the mouse genome shows linkage homology with portions of the human genome [47]. This makes it likely that a QTL mapping result in the mouse will immediately suggest a map location in the human genome, and vice versa. Since QTL mapping is much easier in the mouse, this genetically well-studied laboratory species has become an important tool for mapping human QTL. It is encouraging to note that a number of these QTL are replicable (*ie*, identified in more than one laboratory), and that in the case of five of these murine loci homologous regions in the human genome (indicated by the asterisk) have also been identified.

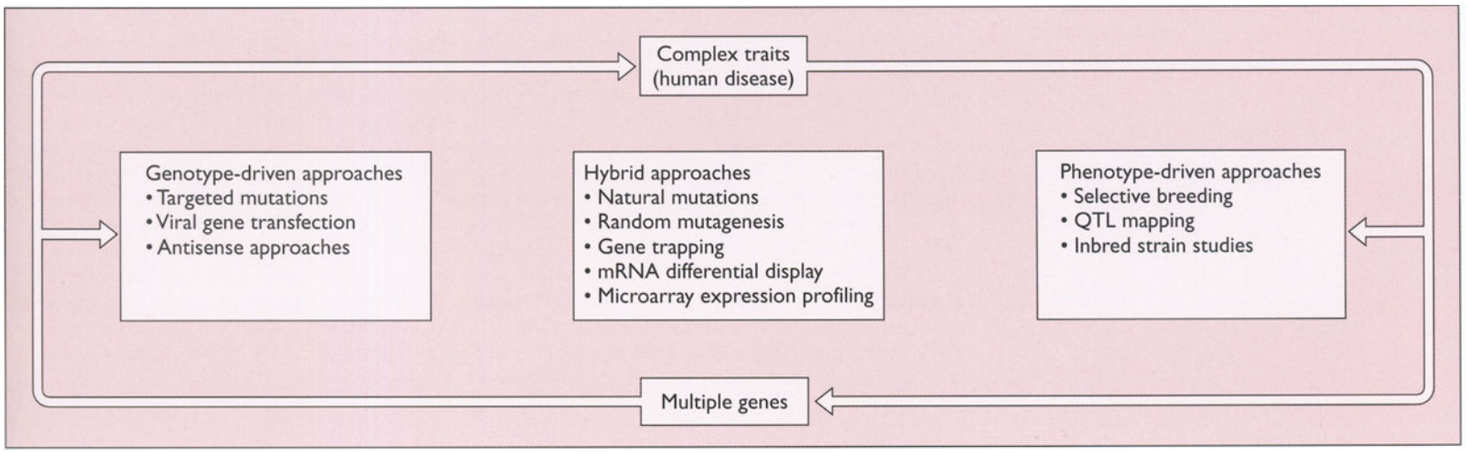



**FIGURE 3-22.** Utility of mouse models in complex traits. Workers investigating determinants of bone mass in humans have limited ability to intervene in the genetics, personal environment, or skeletal biology of their subjects. While association studies can go some way toward implicating a particular genetic locus, they can never be proof of a causal relationship. For this, a functional assay is needed: a way of altering the genetic sequence and seeing whether this modification results in a different phenotype. Such experiments are possible only in animals and may be the sole way of understanding how genetic differences result in individual variation in bone mass [48]. New methods, such as targeted and random mutagenesis, quantitative trait loci (QTL) mapping, and gene expression arrays, as well as classic genetic methods such as artificial selection and the study of inbred strains, are currently being applied to unraveling the complex genetics of osteoporosis and other complex human diseases [49]. Beyond identification of individually important genes, the power of mouse genetics can be exploited to investigate gene-gene interactions (epistasis), composite effects of a single gene (pleiotropism), and the dependence of gene effects on environmental conditions. (*Adapted from* Phillips *et al.* [49].)

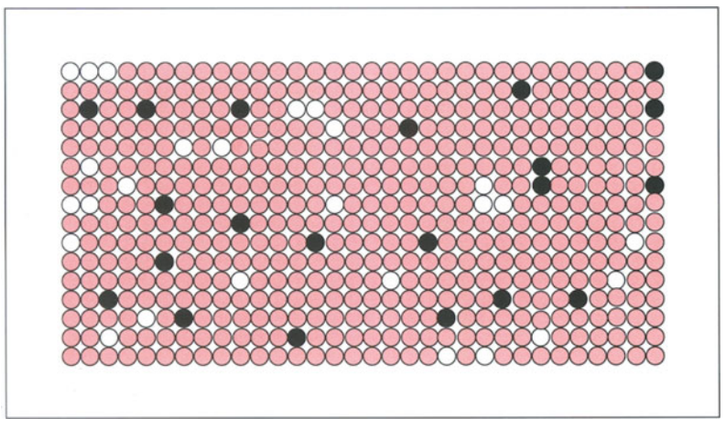


**FIGURE 3-23.** Transcriptional profiling with microarrays. Advances in technology are providing tools that allow for new and abundant levels of information on genome-wide patterns of transcription. A microarray comprises a set of thousands of nucleic acid spots on a solid support. Each spot represents an expressed sequence and consists of an oligonucleotide or cDNA probe. When a labeled cRNA is hybridized to the array, the amount of hybridization to each spot is quantified as an intensity reading that represents individual gene activity. This provides a global picture of gene transcription. The chromosomal region encompassing a quantitative trait locus (QTL) is generally large, containing thousands of genes, and extensive additional work is required to identify the specific gene or genes involved. Recent studies suggest that regulatory variation is important in a variety of complex traits [50]. Quantitative microarray expression studies can reveal regulatory variation in genes for complex traits, including traits for which a priori candidates do not exist. By combining QTL mapping with global expression profiling, it is possible to nominate positional candidate genes for a phenotype of interest [51,52].

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4

# FACTORS THAT INFLUENCE ADULT BONE MASS

*Susan M. Ott*

Adult bone mass is reached between the ages of 20 and 30 years. After that, bone loss due to aging is seen in both genders. In women, bone mass decreases and increases again with each reproductive cycle. At menopause, bone mass decreases rapidly for several years, then the rate slows until the eighth and ninth decade of life, when bone is again lost because bone formation declines even further. Men experience a steadier loss throughout life. Men also show different patterns of loss at the trabecular and cortical surfaces, as well as differences in the relationship between bone formation and bone resorption. The bone mass of African-American men and women is higher than that of whites, but bone mass also decreases with aging in African-Americans.

This chapter focuses on several factors contributing to adult bone loss, including those related to diet, lifestyle, contraception, and reproduction. Exercise, calcium intake, estrogen, and systemic diseases play important roles in bone loss, and these are discussed in other chapters of this book.

Weight is one of the strongest factors associated with bone mass. Weight is related partly to nutrition, is partly under genetic control, and is partly dependent on hormones. Important nutritional factors, in addition to calcium and vitamin D, include protein intake and intake of other vitamins. Although dietary proteins can increase acid load, which has a negative influence on bone mass, they also increase growth factors and improve general nutritional status. In elderly persons, bone mass is positively related to protein intake. Vitamin K is needed for carboxylation of osteocalcin. Vitamin A has been shown to increase bone resorption, and acute toxicity has been well described in the past. Previous studies did not find a negative role of more chronic ingestion of high doses of vitamin A. Recent data, however, suggest that both low and high intakes of vitamin A are harmful to the skeleton.

Smoking and alcohol also influence bone mass. Cigarette smoking causes bone loss, in addition to adverse effects on other body systems. Ethanol, however, has dose-dependent effects. Low intakes are beneficial to bone mass, possibly because ethanol increases estrogen levels. Higher intakes of alcohol are associated with increased fracture risk, owing to inhibitory effects on osteoblasts, increased risk of falls, and associated malnutrition.

In women, reproductive factors contribute to bone mass. Pregnancy has modest effects on the net change in bone mass, but losses with lactation, averaging 1% per month, are higher than those experienced during menopause. The recovery phase after weaning represents a time of rapid increase in bone mass, similar to that seen during adolescence. Contraceptive choices also have effects on bone mass; hormonal agents, such as depo-medroxyprogesterone acetate, cause decreases in bone density, which may be reversible. The effects of oral contraceptives require further study.

# Aging and Gender

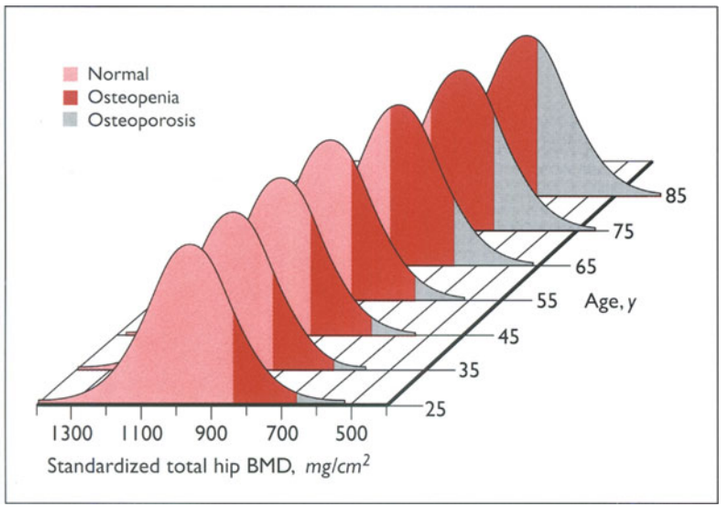



**FIGURE 4-1.** The inexorable loss of bone with aging. The normal distribution at age 25 years is the basis for the current World Health Organization definitions of osteoporosis and osteopenia. Whereas fewer than 1% of young white women have osteoporosis, about 40% of elderly women have bone density in the osteoporotic range. The graph shows standardized bone density of the total hip measured by dual-energy x-ray absorptiometry. Although bone mineral density (BMD) is normally distributed at all ages, it gradually declines as age increases. The *lightly shaded area* shows the proportion of subjects with osteopenia, and the *darkly shaded area* the proportion with osteoporosis. (*Data from* Looker *et al.* [1].)

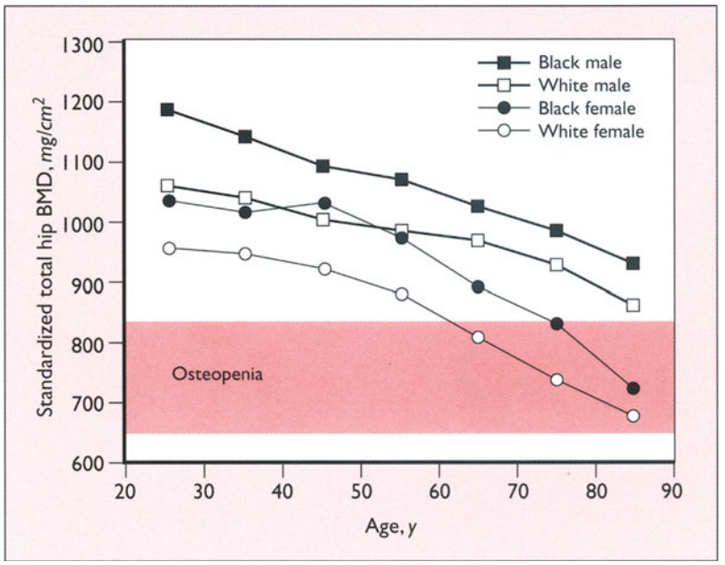
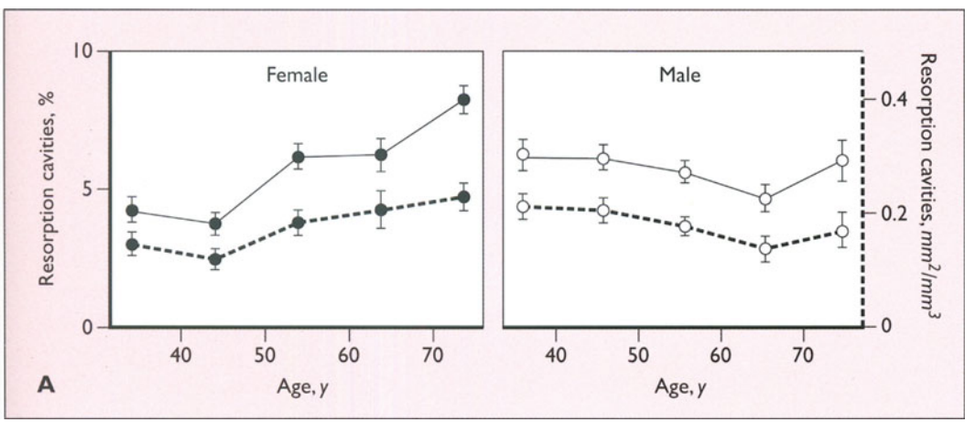



**FIGURE 4-2.** Standardized total hip bone mineral density (BMD) by dual-energy x-ray absorptiometry showing the average values for African-American and white men and women. Both genders and races show bone loss with aging. (*Data from* Looker *et al* [1].)



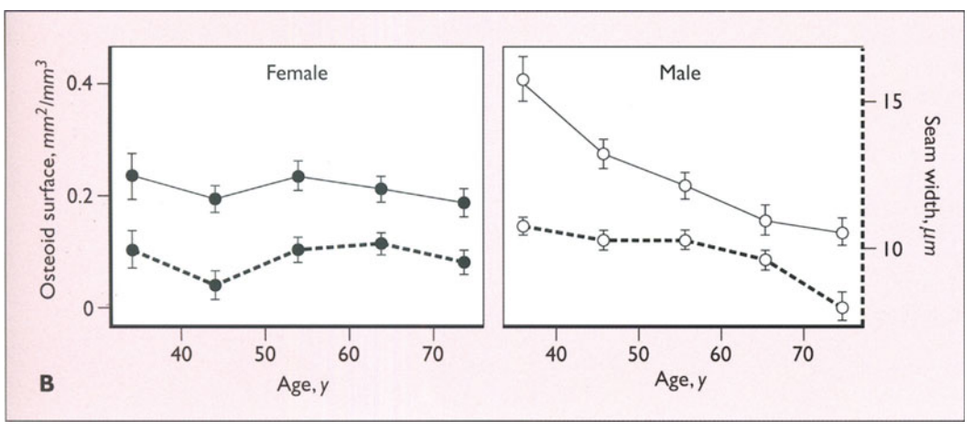




**FIGURE 4-3.** Sex differences in trabecular bone with aging (**A—C**). A loss of trabecular bone with age is common to both sexes and similar in extent. Significant differences in static indices of remodeling, however, can be demonstrated between the sexes. In men, the extent of resorption cavities changes little with age when expressed either in absolute terms or as a percentage of total trabecular surface. In contrast, in women, an increase from initially low levels is apparent by the sixth decade. In women, the extent of osteoid borders (a reflection of bone-forming activity) shows little change with age in absolute or relative terms. Conversely, in men, progressive decline occurs in both absolute and relative terms. The decrease in osteoid tissue in aging men is also associated with a decline not only in mean wall thickness but also in both lamellar number and width. These changes were not seen in the women, in whom the variables remained almost constant. From these findings, it can be concluded that in the aging woman increased bone resorption occurs, resulting in a perforation and loss of trabeculae. In the aging man, however, it appears that the structure of the trabecular network is largely maintained while the width of trabeculae diminishes as the result of decreased bone formation. *Dashed lines*—read the values on the right; *solid lines*—read the values on the left; SE—standard error. (*Adapted from* Aaron *et al.* [2].)

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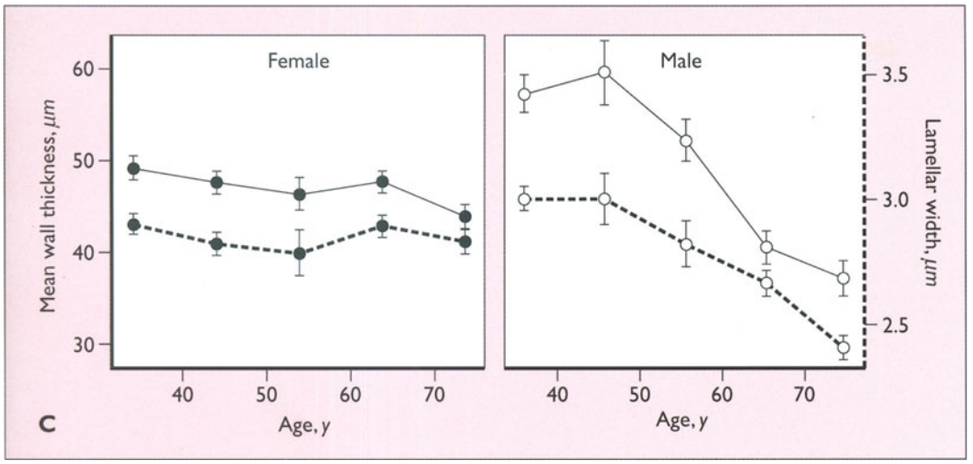



**FIGURE 4-3.** *(Continued)*

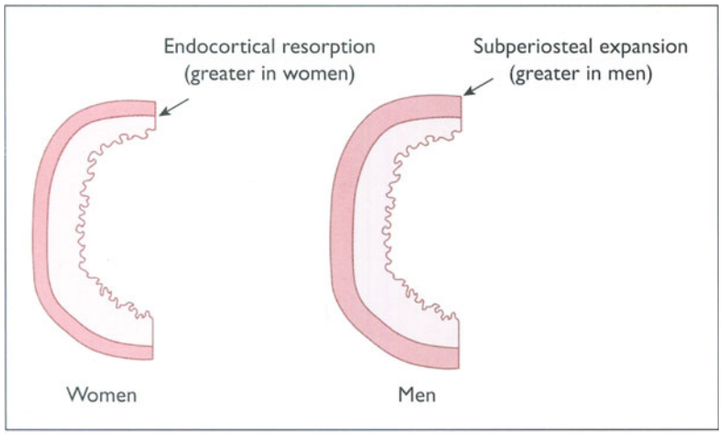



**FIGURE 4-4.** Sex differences in cortical bone remodeling with age. The diminution in cortical bone density is less in men because endocortical bone resorption is less and periosteal appositional growth is greater. The greater periosteal bone formation may be a more important means of preserving bone strength than is the lesser endosteal bone resorption because the accumulation of bone distant from the neutral or long axis of bone is biomechanically advantageous. This greater age-related increase in periosteal bone formation in men than in women has been shown for the vertebral body, proximal femur, and midtibia. (*Adapted from* Ruff and Hayes [3].)

## Clinical Factors That Affect Bone Mass

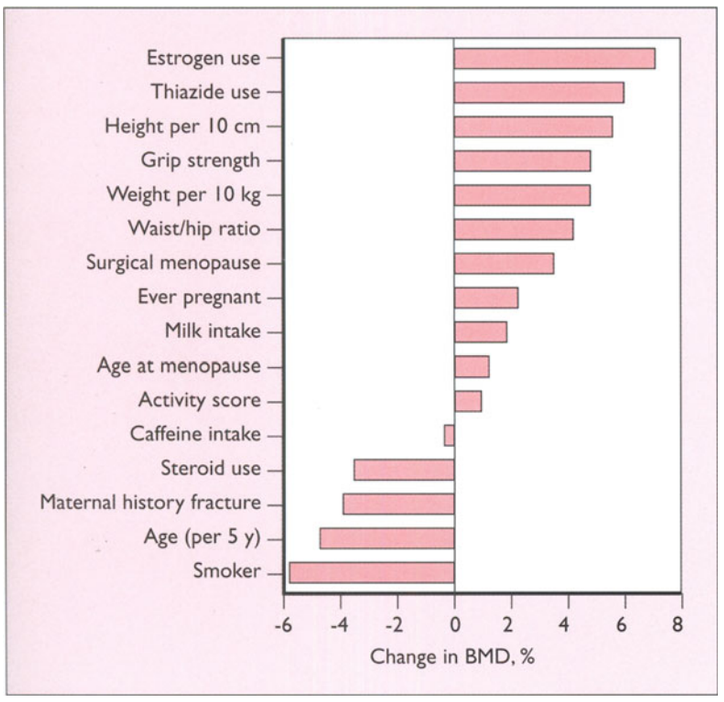



**FIGURE 4-5.** These are baseline data from the 9704 women in the Study of Osteoporotic Fractures. They were ambulatory women older than 65 years, and most were white. The graph shows the percentage difference in the bone mineral density (BMD) comparing women who had a risk factor to the group's mean BMD (in the case of categorical variables). For continuous variables, the graph shows the difference in bone density for approximately 1 standard deviation change in the variable. For example, on average, a woman who uses thiazide diuretics has bone density 6% higher than one who does not use thiazides. Similarly, the average BMD decreased about 5% for every 5-year increase in age. (*Data from* Bauer *et al.* [4].)

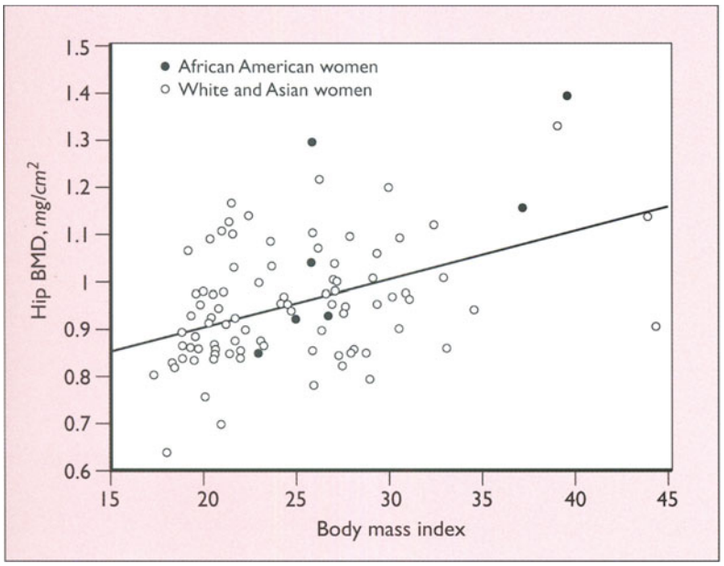



**FIGURE 4-6.** Weight is one of the most important factors related to bone mass. The figure shows the relationship between body mass index and total hip bone mineral density (BMD) (measured by dual-energy x-ray absorptiometry [DEXA]) in normal women aged 18 to 40 years in mg/cm$^2$. The *black circles* represent African-American women and the *red circles* are white or Asian women. Weight itself is even more strongly correlated to the bone density, but weight is related to both fatness and body size. The DEXA measures the amount of mineral within a projected area; thus, bones that are larger will have greater BMD, even when the actual bone density (in three dimensions) is the same. In part, the body mass index reflects the contribution of body fat, which may be related to leptin levels. (*Unpublished data from* study reported by Scholes *et al.* [5].)

## Nutritional Factors

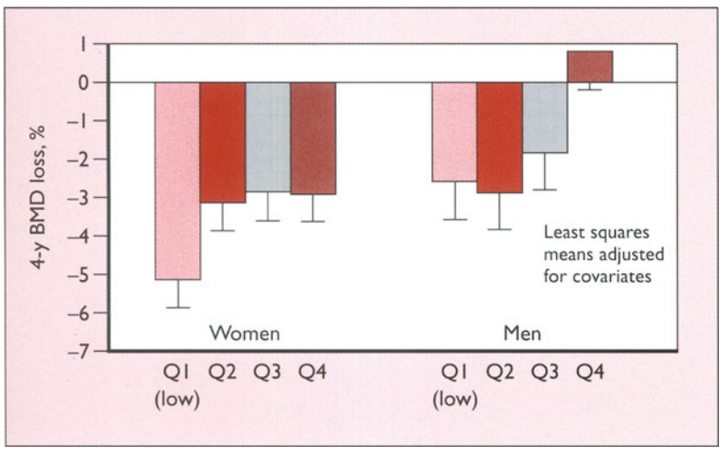



**FIGURE 4-7.** Protein intake and bone loss in elderly men and women. Evidence suggests that protein undernutrition may be associated with osteoporotic fractures. In contrast, evidence also exists that diets rich in animal protein may actually result in negative calcium balance, which would result in acceleration of bone loss. These considerations notwithstanding, there have been few longitudinal studies of protein intake and bone loss among older persons, who may be consuming less protein than the high amounts previously linked to negative calcium balance. Such an evaluation was recently completed as part of the Framingham Osteoporosis Study. Four-year longitudinal data on dietary intake and bone mineral density (BMD) were collected on 391 women and 274 men who were members of the original Framingham Heart Study. Both men and women in the lowest quartile of protein intake had greater losses of bone mass at the femoral neck than did those in the highest quartile of protein intake. This was true after adjustment for multiple covariates, including age, weight, cigarette smoking, caffeine intake, calcium intake, physical activity, alcohol consumption, and estrogen replacement therapy in women. (*Adapted from* Hannan *et al.* [6].)

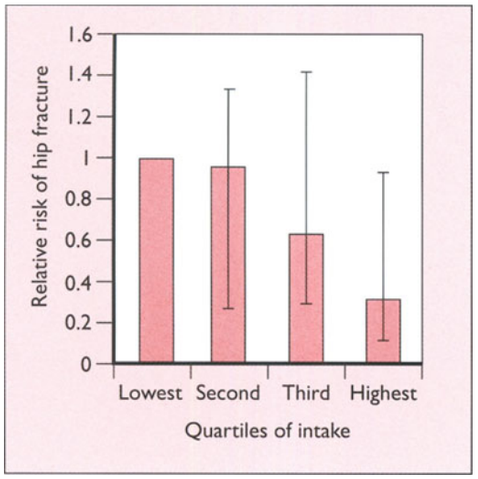



**FIGURE 4-8.** Risk of hip fracture according to animal protein intake in postmenopausal women. Data are from a study of 104,338 person-years, showing the 95% confidence intervals using a multivariate model that included body size. (*Data from* Munger *et al.* [7].)

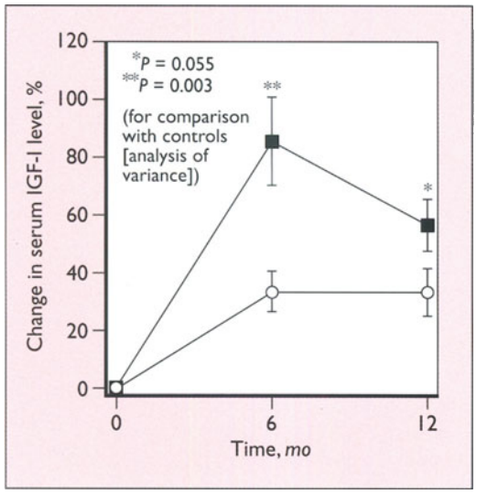



**FIGURE 4-9.** Protein supplementation in patients with hip fracture improves bone mass. Protein restriction has been shown to reduce plasma levels of insulin-like growth factor-I (IGF-I) by inducing resistance to the action of growth hormone in the liver and increasing the metabolic clearance rate of the growth factor. Thus, low protein intake in elderly persons, such as those recovering from hip fracture, may be detrimental to skeletal health. In a recent randomized controlled trial of a protein supplement given to patients recuperating from hip fracture ($n$ = 41 treated; 41 in the control group), supplements increased IGF-I levels significantly and slowed the loss of bone mineral density compared with placebo. The *solid square* represents patients who received protein supplements; the *open circle* represents patients in the control group. (*Adapted from* Schurch *et al.* [8].)

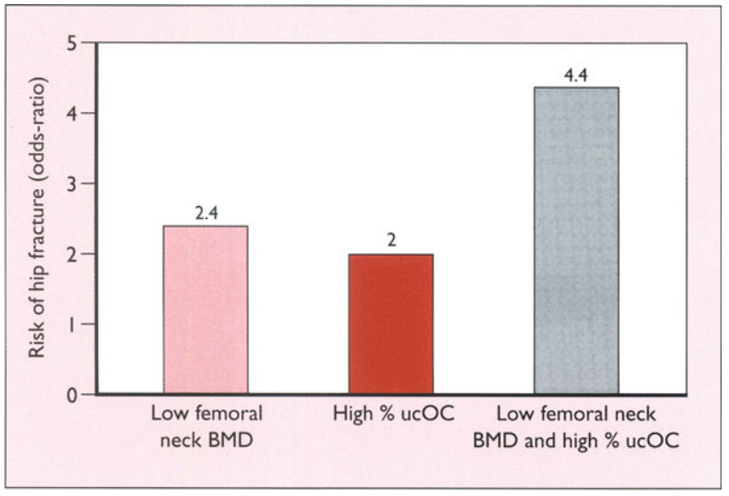



**FIGURE 4-10.** Bone mineral density (BMD) and undercarboxylated osteocalcin levels to predict hip fracture. The undercarboxylation of osteocalcin resulting from vitamin K deficiency has been hypothesized to affect bone mass because vitamin K plays an important role in the gamma-carboxylation of glutamic acid residues in pro-osteocalcin, which is essential for the mineralization of osteoid. Vergnaud *et al.* [9] studied 104 elderly women with hip fracture, using 25 women (average age, 82 years) without hip fracture as the control group. Both low femoral neck BMD (lowest quartile) and high levels of undercarboxylated osteocalcin (ucOC, highest quartile) were equal predictors of fracture. The women with both low BMD and high ucOC were at the highest risk for hip fracture. (*Adapted from* Vergnaud *et al.* [9].)

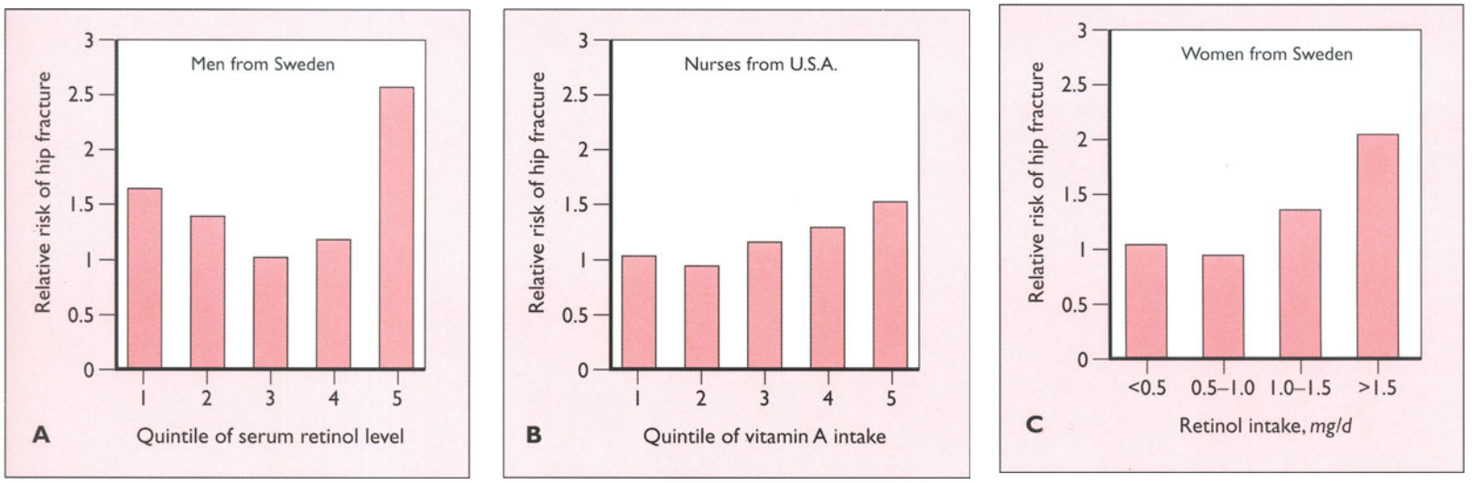
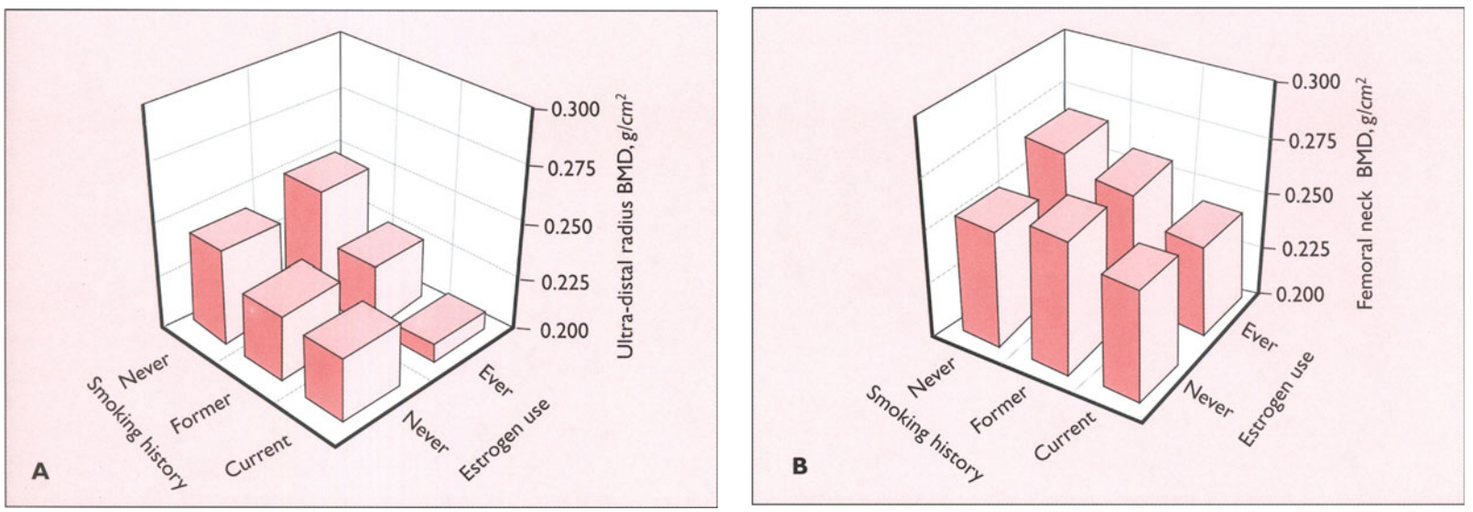



**FIGURE 4-11.** Data from three recent studies of vitamin A intake. **A,** Data from 2322 Swedish men. There was a significant increase in the relative risk of hip fracture in those with the highest quintile of serum retinol. **B,** Results from a study of 72,337 American nurses, who had a higher risk of hip fracture with greater vitamin A intake. **C,** Data from 175 Swedish women, in whom the highest quartile of retinol intake was associated with a higher risk of hip fracture. A fourth recent study (*not shown*) from Rancho Bernardo [10] showed that bone mineral density in elderly men and women was related to vitamin A intake in a U-shaped curve; both deficiency and excess were associated with lower bone mass. The best bone mineral density was seen at the recommended intake of vitamin A. (*Data from* Michaelsson *et al.* [11], Feskanich *et al.* [12], and Melhus *et al.* [13].)

## Smoking, Alcohol, and Bone



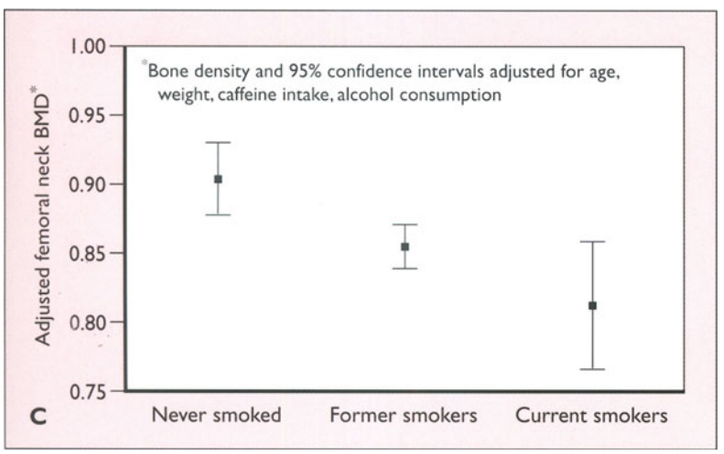




**FIGURE 4-12. A** and **B,** Deleterious effects of cigarette smoking on the skeleton in women. The negative effects of smoking cigarettes on skeletal health have long been recognized; however, not all the results of studies have been in agreement. One possible factor that may interact with cigarette smoking in women is estrogen status. Cigarette smoking accelerates the 2-hydroxylation of estrone to an inactive metabolite, 2-hydroxyestrone; thus, a biologic mechanism exists that may explain why women who take estrogen replacement therapy (ERT) and smoke have a lower bone mineral density (BMD) than that of women who take ERT and do not smoke. Women who had used ERT had higher BMD than that of nonusers only if they had never smoked. The use of ERT did not confer any advantage in BMD among current smokers. **C,** The deleterious effects of smoking cigarettes on the skeleton in men. In men, cigarette smoking clearly results in lower BMD. In this study of 348 elderly men, current smokers had lower BMD at the femoral neck than that of those who did not smoke. (*Adapted from* Kiel *et al.* [14].)

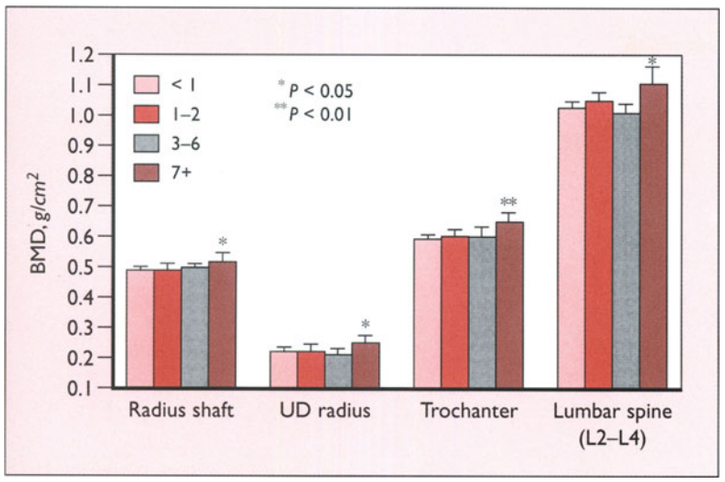



**FIGURE 4-13.** Moderate alcohol intake is associated with increased bone mineral density (BMD). Although persons who are alcoholics suffer from osteoporosis and increased risk of fracture, the consumption of lesser amounts of alcohol may favorably impact the skeletal status of women. One mechanism for this may be the recognized effects of alcohol on increasing endogenous estrogen levels or even adrenal androgen levels. In this study of 384 women, BMD was higher in those who drank at least 7 oz/wk of alcohol than it was in those who drank less than 1 oz/wk. This difference was not explained by differences in age, weight, height, age at menopause, smoking cigarettes, and years of estrogen replacement therapy, which were adjusted for in this analysis. UD—ultra-distal. (*Adapted from* Felson *et al.* [15].)

## Pregnancy

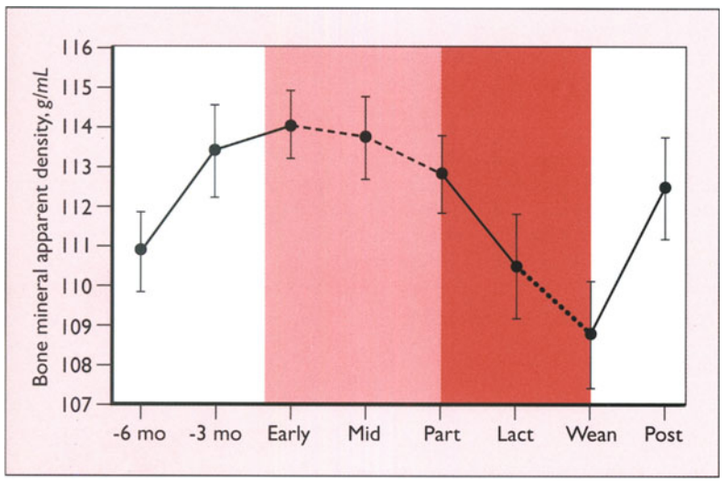



**FIGURE 4-14.** A longitudinal study of bone mineral density in a primate model. This graph shows bone mineral density in the spine, measured by dual-energy x-ray absorptiometry and adjusted for three dimensions to avoid size artifact. These young animals were still growing (analogous to adolescent humans). During pregnancy (*light shading*), bone mineral density stopped increasing and began to show a loss. Lactation (*dark shading*) was associated with a significant decrease in bone density, which promptly recovered after weaning. Bone biopsies were done at the middle of pregnancy and at weaning, and demonstrated a reduced bone formation rate at midpregnancy and an increased bone formation at weaning. -6 mo, -3 mo—months prior to conception; early—early pregnancy; mid—midpregnancy; part—parturition; lact—lactation; post—postweaning. (*Adapted from* Ott *et al.* [16].)

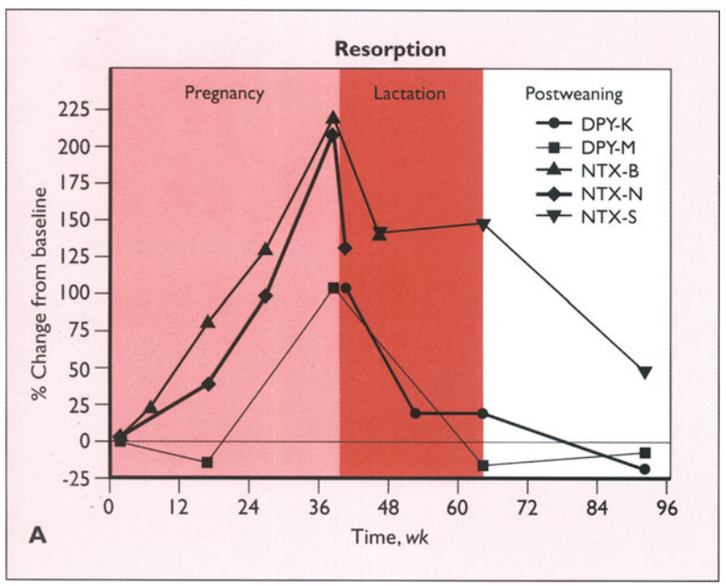



**FIGURE 4-15.** Graphs showing several longitudinal studies of human pregnancy and lactation. All the data have been converted to percent change from baseline. In the studies that began after delivery, the baseline from one of the studies of pregnancy was used. **A,** Markers of bone resorption (DPY—deoxypyridinoline; NTX—N-telopeptide). During the first trimester of pregnancy, bone resorption increased a small amount, increasing to very high levels during the last trimester. Resorption remained high during early lactation, and then started to decline. After weaning, resorption returns to baseline levels.

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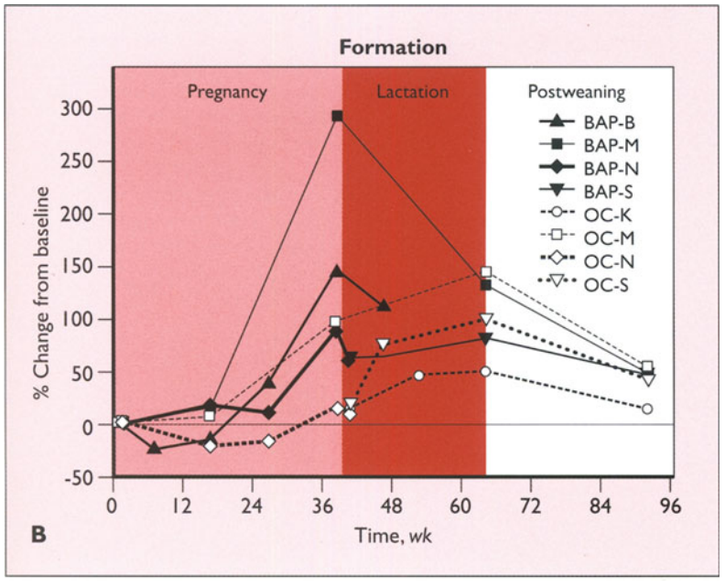


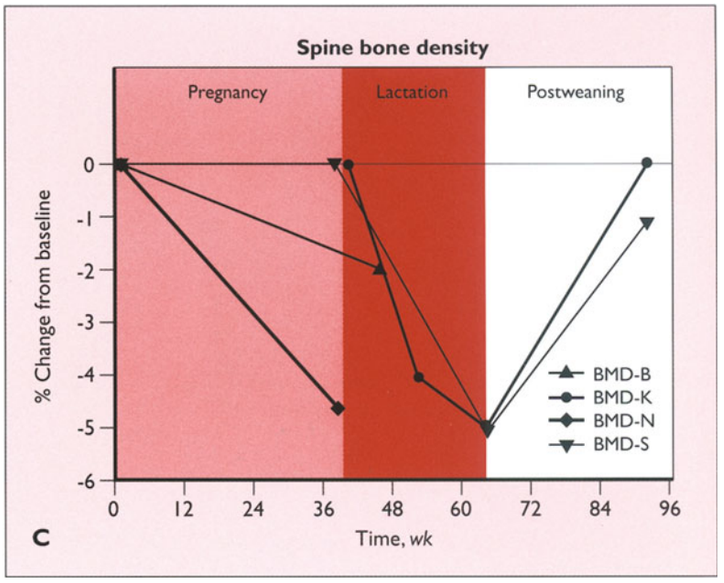


**FIGURE 4-15.** *(Continued)* **B,** Markers of bone formation. BAP—bone alkaline phosphatase; OC—osteocalcin. These values are unchanged or depressed during the first half of pregnancy, and then start to increase. The data on bone alkaline phosphatase during lactation are variable, but all studies show a return toward baseline following weaning. **C,** Bone mineral density (BMD) of the spine by dual-energy x-ray absorptiometry. Studies during pregnancy are variable, but losses during lactation approach 1% per month. As in the primates, rapid recovery is seen after weaning. (*Data from* studies by Black *et al.* [17], Sowers *et al.* [18–20], Kalkwarf *et al.* [21,22], More *et al.* [23], and Naylor *et al.* [24].)

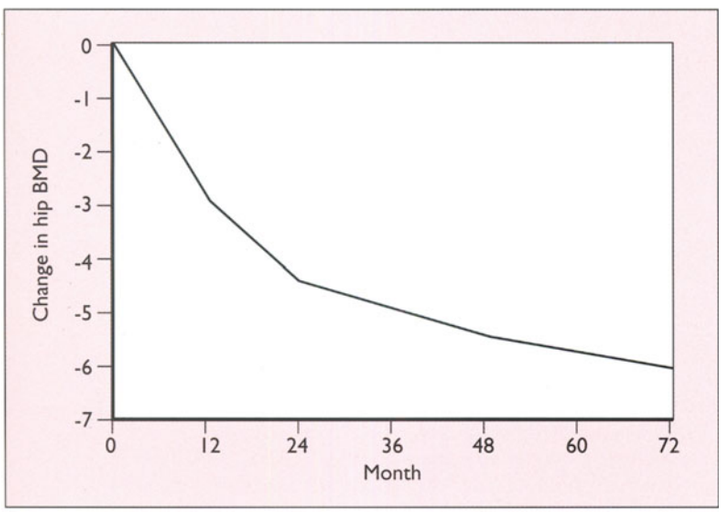


**FIGURE 4-16.** Loss of bone mineral density (BMD) in women using depo-medroxyprogesterone acetate for contraception. Average percent changes are derived from a longitudinal study that involved measures of bone density every 6 months in women using this form of contraception. Women entered the study with varying durations of prior depo-medroxyprogesterone use, and bone loss was most rapid in those who were just beginning the medication. (*Data from* Scholes *et al.* [5].)

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5

# Epidemiology of Osteoporosis and Associated Fractures

*Loran M. Salamone*

Osteoporosis is a metabolic bone disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk [1]. Osteoporosis is the most prevalent metabolic bone disease in the United States and in other developed countries. In the United States, as many as 54% (16.8 million) of postmenopausal white women have low bone mass or osteopenia and another 30% (9.4 million) have osteoporosis. Among 50-year-old white women and men, the estimated lifetime fracture risk is 40% in women and 13% in men [2].

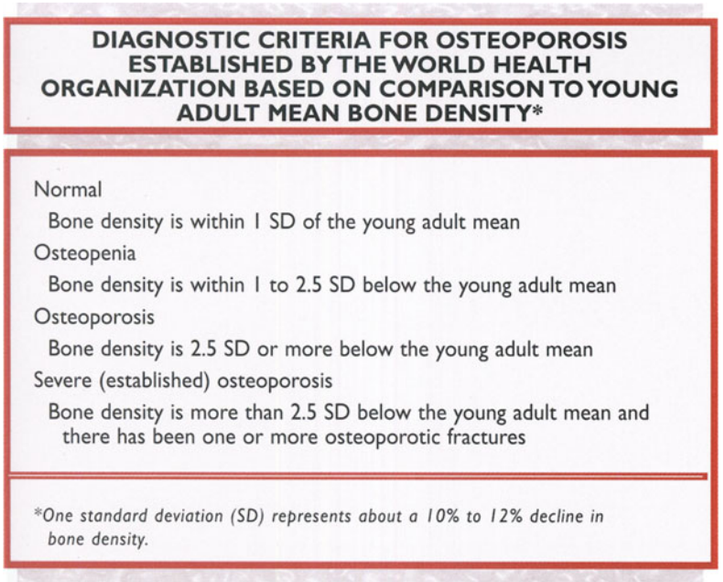
Osteoporotic fractures are directly related to age, with a rising incidence of fractures in women starting at about the age of 50 years. In women, the incidences of most fractures increase with age after menopause [3]; a similar age-related increase is seen in men, although the total number of fractures is approximately half that seen in women [4]. Hip fractures result in the highest morbidity and mortality, with a mortality rate of 10% to 20% during the first year following a fracture, with most of the deaths occurring within 6 months of the fracture [5].

The risk of osteoporosis can be defined in terms of bone mineral density (BMD) or by the occurrence of fractures. Bone mineral density is a useful risk factor by which to categorize people according to the degree of fracture risk. Bone density measurements are safe and noninvasive and not only can assess differences in risk between individuals but also can monitor changes in risk within individuals over time. BMD is essential in predicting the risk of fracture and monitoring the progress of intervention strategies. It has been estimated that a decline of 1 standard deviation in BMD is equivalent to a 1.5-fold to 2.5-fold increase in fracture risk for women and men [6,7].

Alternatively, one can describe the impact of osteoporosis by assessing the prevalence and incidence of fractures. *Prevalence* refers to the number of people in the population who at a given time have already had fractures related to osteoporosis, whereas *incidence* refers to the number of new fractures occurring in a population within a specified period of time. Osteoporosis fractures are characterized by higher incidence rates among women than among men, rates that increase sharply with age, and a greater propensity for fractures in skeletal sites containing large amounts of cancellous bone [8]. The hip, spine, and distal forearm, which share these characteristics, are recognized as the most common sites affected in osteoporosis. Most fractures in older women are, in fact, due to low bone mass [9]. Since bone loss is an asymptomatic process, diagnosis often is made only after fracture has occurred. It is critical to gain a broader recognition of the extent of this public health problem to facilitate earlier detection, prevention, and better management of this increasingly important disease among the increasing elderly population.

This chapter summarizes epidemiologic data related to the frequency of osteoporosis and its related fractures, and discusses the societal impact of this disease. More specifically, it focuses on the magnitude of the health problem, encompassing prevalence and incidence patterns of both low bone mass and fractures across cultural groups; the evaluation of fracture risk, including an overview of identifiable risk factors, the role of bone density, and the risk of falling; and the economic consequences of osteoporotic fractures.

# Epidemiology of Osteoporosis



**DIAGNOSTIC CRITERIA FOR OSTEOPOROSIS ESTABLISHED BY THE WORLD HEALTH ORGANIZATION BASED ON COMPARISON TO YOUNG ADULT MEAN BONE DENSITY***

Normal
- Bone density is within 1 SD of the young adult mean

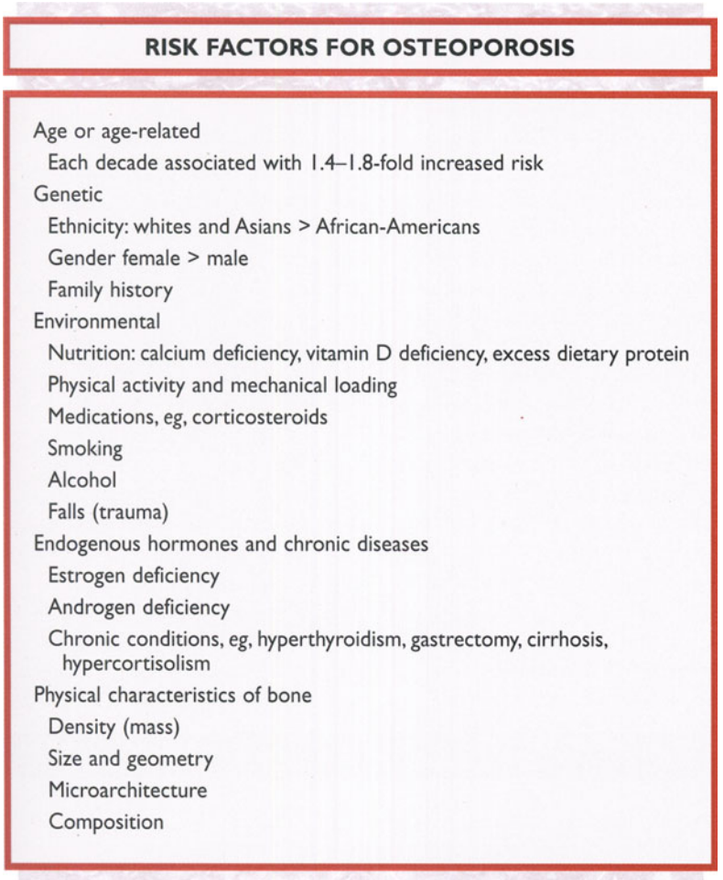
Osteopenia
- Bone density is within 1 to 2.5 SD below the young adult mean

Osteoporosis
- Bone density is 2.5 SD or more below the young adult mean

Severe (established) osteoporosis
- Bone density is more than 2.5 SD below the young adult mean and there has been one or more osteoporotic fractures

*One standard deviation (SD) represents about a 10% to 12% decline in bone density.

**FIGURE 5-1.** Diagnostic criteria established by the World Health Organization based on comparison to young adult mean bone density. (*Adapted from* Kanis *et al.* [10].)



**RISK FACTORS FOR OSTEOPOROSIS**

Age or age-related
- Each decade associated with 1.4–1.8-fold increased risk

Genetic
- Ethnicity: whites and Asians > African-Americans
- Gender female > male
- Family history

Environmental
- Nutrition: calcium deficiency, vitamin D deficiency, excess dietary protein
- Physical activity and mechanical loading
- Medications, eg, corticosteroids
- Smoking
- Alcohol
- Falls (trauma)

Endogenous hormones and chronic diseases
- Estrogen deficiency
- Androgen deficiency
- Chronic conditions, eg, hyperthyroidism, gastrectomy, cirrhosis, hypercortisolism

Physical characteristics of bone
- Density (mass)
- Size and geometry
- Microarchitecture
- Composition

**FIGURE 5-2.** Risk factors for osteoporosis. (*Adapted from* Wasnish [11].)

**CANDIDATE GENES THAT HAVE BEEN STUDIED IN RELATION TO BONE MASS**

| Category | Candidate Gene |
|---|---|
| Calciotropic hormones and receptors | VDR |
| | ER |
| | Aromatase |
| | PTH |
| | PTHR1 |
| | Calcitonin receptor |
| | Glucocorticoid receptor |
| | Calcium-sensing receptor |
| Cytokines, growth factors, and receptors | TGFB-1 |
| | IGF-I |
| | IL-6 |
| | IL-1B |
| | IL-1RA |
| | TNFR2 |
| | BMP-4 |
| Bone matrix | COLIA1 |
| | Osteocalcin |
| | Collagenase |
| | Alpha HS2 glycoprotein |
| Miscellaneous | ApoE |
| | MTHFR |
| | P57 Kip |
| | HLA |
| | PPAR gamma |
| | Werner helicase gene |

**FIGURE 5-3.** Candidate genes that have been suggested in the regulation of bone mass or osteoporotic fractures. Osteoporosis is a disease with a strong genetic component. Candidate gene studies have investigated cytokines and growth factors that regulate bone turnover, genes that encode components of bone matrix, and genes that encode receptors for calciotropic hormones. ApoE—apolipoprotein E; BMP-4—bone morphogenetic protein 4; HLA—human leukocyte antigen; IGF-I—insulin-like growth factor I; IL-1RA—interleukin-1 receptor antagonist; MTHFR—methyltetrahydrofolate reductase; PPAR—peroxisome proliferator activated receptor; PTHR1—parathyroid hormone receptor type 1; TGFB-1—transforming growth factor beta 1; TNFR2—tumor necrosis factor receptor type 2. (*Adapted from* Ralston *et al.* [12].)

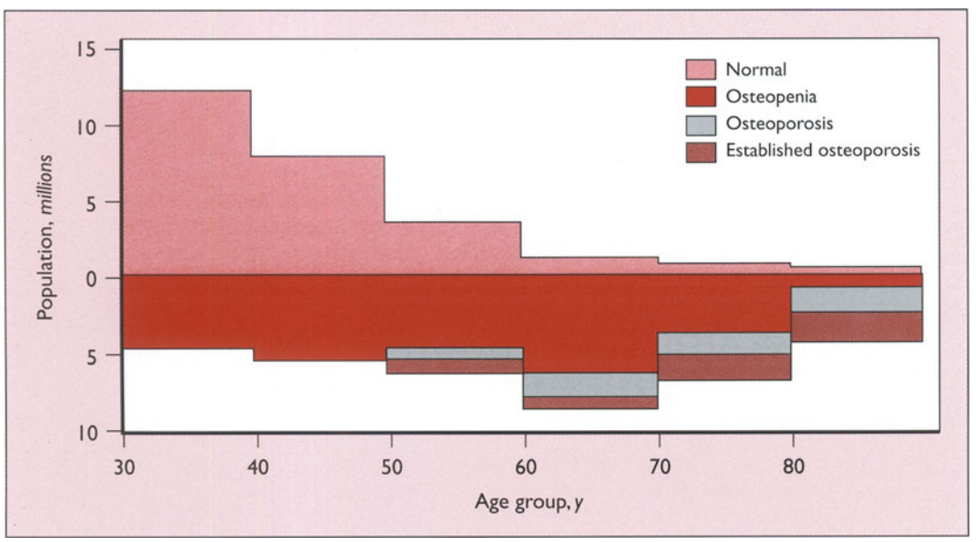



**FIGURE 5-4.** Estimated skeletal status of white women in the United States in 1990 by age group. *Osteopenia* is bone density of the hip, spine, or distal forearm more than 1.0 but less than 2.5 standard deviations (SD) below the mean in young adults (ages 30–40 years). *Osteoporosis* is bone density at one or more of these sites more than 2.5 SD below the young adult mean (ages 30–40 years). *Established osteoporosis* is bone density at one or more of these sites more than 2.5 SD below the young adult mean and at least one osteoporotic fracture. Numbers above the middle line 0 represent women with normal bone density, numbers below the middle line represent the women in the three categories of osteopenia and osteoporosis. Most women under age 50 years have normal bone density at all four skeletal sites, although with advancing age, a greater proportion have osteopenia or osteoporosis. At age 80 years and over, only 3% have normal bone density at all four sites, 27% have osteopenia at one skeletal site or another, and 70% have osteoporosis. (*Adapted from* Cooper and Melton [8].)

**PROPORTION (%) OF ROCHESTER, MINNESOTA, WOMEN WITH BONE MINERAL MEASUREMENTS MORE THAN 2.5 STANDARD DEVIATIONS BELOW THE MEAN FOR YOUNG NORMAL WOMEN**

| Age Group, y | Lumbar Spine, % | Either Hip Site, % | Midradius, % | Spine, Hip, or Midradius, % |
|---|---|---|---|---|
| 50–59 | 7.6 | 3.9 | 3.7 | 14.8 |
| 60–69 | 11.8 | 8.0 | 11.8 | 21.6 |
| 70–79 | 25.0 | 24.5 | 23.1 | 38.5 |
| ≥80 | 32.0 | 47.5 | 50.0 | 70.0 |
| Total | 16.5 | 16.2 | 17.4 | 30.1 |

**FIGURE 5-5.** Proportion of women in Rochester, Minnesota, with bone mineral measurements more than 2.5 standard deviations below the mean for young normal women. The mean is derived from 48 subjects younger than 40 years of age, who were randomly sampled from the Rochester, Minnesota, population. None of them were known to have any disorder that might influence bone metabolism. The total is age-adjusted to the population structure of 1990 United States white women 50 years of age and older. (*Adapted from* Melton [3].)

**PREVALENCE OF LOW FEMORAL BONE DENSITY IN NONINSTITUTIONALIZED UNITED STATES WOMEN AGED 50 AND OLDER (NHANES III 1988–1994)**

| | Osteoporosis | | |
|---|---|---|---|
| Region of Interest | Prevalence* | 95% CI† | Millions‡ |
| Non-Hispanic whites | | | |
| Femur neck | 20(17) | 17,22 | 6 |
| Trochanter | 13(12) | 11,15 | 4 |
| Intertrochanter | 15(13) | 13,17 | 4 |
| Total femur | 17(15) | 15,19 | 5 |
| Non-Hispanic blacks | | | |
| Femur neck | 5(6) | 4,7 | 0.2 |
| Trochanter | 7(7) | 5,8 | 0.2 |
| Intertrochanter | 7(7) | 5,10 | 0.2 |
| Total femur | 8(8) | 6,10 | 0.3 |
| Mexican Americans | | | |
| Femur neck | 10(14) | 7,13 | 0.1 |
| Trochanter | 12(15) | 7,16 | 0.1 |
| Intertrochanter | 11(14) | 7,14 | 0.1 |
| Total femur | 12(16) | 8,16 | 0.1 |

**Prevalences shown in parenthesis are age-adjusted to the 1980 US census population.*

*†Pertain to unadjusted prevalences.*

*‡Based on the average of undercount-adjusted population estimates from the March 1990 and March 1993 Current Population Surveys.*

**FIGURE 5-6.** Prevalence of low femoral bone density in noninstitutionalized United States women aged 50 years and older, according to NHANES III 1988–1994. CI—confidence interval. (*Adapted from* Looker *et al.* [13].)

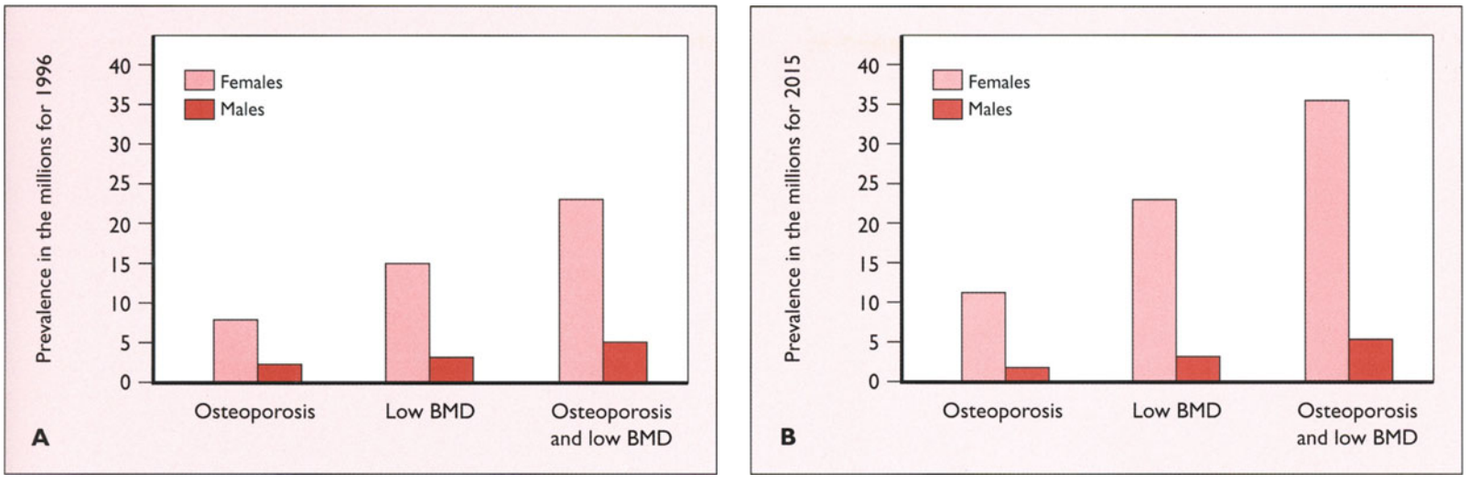



**FIGURE 5-7.** For this study, *osteoporosis* was defined as femoral bone density values more than 2.5 standard deviations (SD) below those of a non-Hispanic, white female reference group mean age 20 to 29 years. *Low bone mass* was defined as bone density values between 1 and 2.5 SD below a non-Hispanic, white female reference group (mean age 20–29 years). Research summaries from NHANES III were used as the basis for extrapolations of prevalence data. **A**, Osteoporosis prevalence figures for 1996 in the United States population of women and men aged 50 years and older [14]. Osteoporosis: women = 8,021,036; men = 2,081,950. Low bone mass or osteopenia: women = 15,434,059; men = 3,122,926. Total women and men with osteoporosis and low bone mass: women = 23,455,096; men = 5,204,875. **B**, Estimated prevalence of osteoporosis for 2015 in the United States population of women and men aged 50 years and older. Osteoporosis: women = 11,914,236; men = 2,461,927. Low bone mass, or osteopenia: women = 23,115,835; men = 2,461,927. Total with osteoporosis and low bone mass: women = 35,030,069; men = 6,154,825. BMD—bone mineral density. (*Data from* National Osteoporosis Foundation [15].)

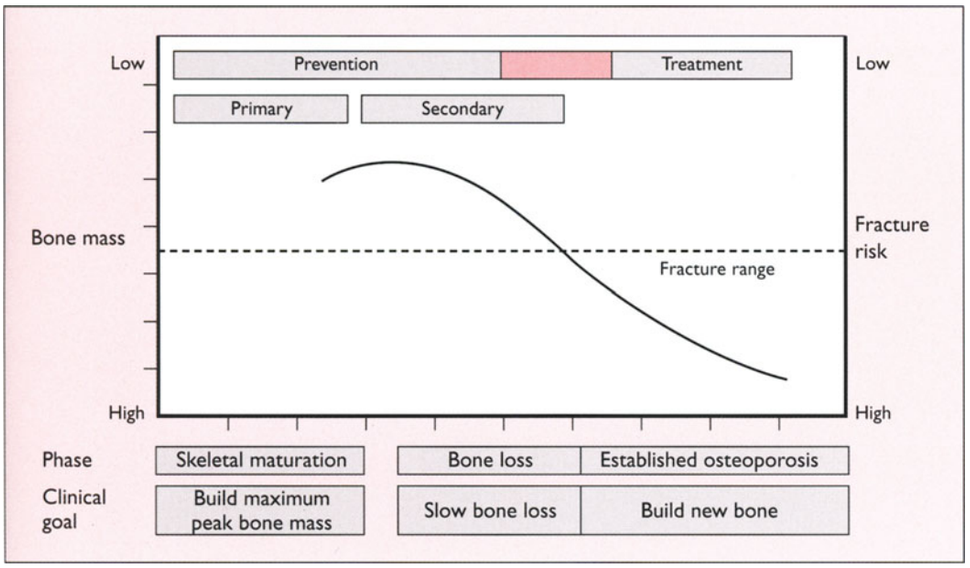



**FIGURE 5-8.** Bone mass and risk of fracture over the lifespan. (*Adapted from* Wasnish [11].)

# Fracture Epidemiology

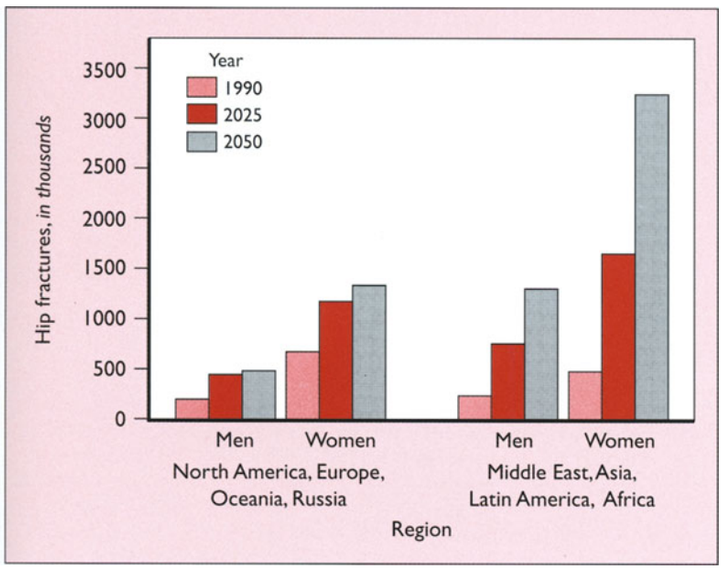



**FIGURE 5-9.** The estimated number of fractures (in thousands) for men and women in different regions of the world in 1990, 2025, and 2050. The number of hip fractures worldwide is projected to increase from 1.66 million in 1990 to 6.26 million by 2050. Currently, about half of all hip fractures occur in Europe and North America; by 2050 these regions will account for only one fourth of the total, and the majority of hip fractures are expected to occur in Asia and Latin America. (*Adapted from* Cooper *et al.* [16].)

**INCIDENCE OF HIP FRACTURE (RATES PER 100,000) IN 1990 BY AGE, SEX, AND REGION**

| Region | Men: Age, y | | | | | | |
|---|---|---|---|---|---|---|---|
| Europe | 50–54 | 55–59 | 60–64 | 65–69 | 70–74 | 75–79 | 80+ |
| Western Europe | 28 | 33 | 67 | 103 | 203 | 331 | 880 |
| Southern Europe | 10 | 16 | 34 | 55 | 81 | 190 | 534 |
| Eastern Europe | 38 | 38 | 88 | 88 | 194 | 194 | 475 |
| Northern Europe | 58 | 66 | 97 | 198 | 382 | 682 | 1864 |
| North America | 33 | 33 | 81 | 123 | 119 | 338 | 1230 |
| Oceania | 20 | 34 | 63 | 92 | 180 | 445 | 1157 |
| Asia | 19.5 | 19.5 | 36.5 | 46.5 | 102 | 150 | 364 |
| Africa | 6.0 | 10.0 | 14.0 | 27.0 | 8.0 | 0 | 116 |
| Latin America | 25 | 40 | 40 | 106 | 106 | 327 | 327 |
| World | 22.5 | 24.5 | 47.3 | 68.7 | 119.1 | 219.4 | 630.2 |
| | **Women: Age, y** | | | | | | |
| Europe | 50–54 | 55–59 | 60–64 | 65–69 | 70–74 | 75–79 | 80+ |
| Western Europe | 33 | 54 | 115 | 184 | 362 | 657 | 1808 |
| Southern Europe | 11 | 21 | 47 | 100 | 170 | 380 | 1075 |
| Eastern Europe | 58 | 58 | 155 | 155 | 426 | 426 | 1251 |
| Northern Europe | 74 | 78 | 190 | 327 | 612 | 1294 | 2997 |
| North America | 60 | 60 | 117 | 252 | 437 | 850 | 2296 |
| Oceania | 31 | 63 | 112 | 204 | 358 | 899 | 2476 |
| Asia | 14 | 14 | 38 | 74.5 | 155.5 | 252 | 562.5 |
| Africa | 4.0 | 12 | 17 | 12 | 16 | 50 | 80 |
| Latin America | 19.5 | 50 | 50 | 162.5 | 162.5 | 622 | 622 |
| World | 23.9 | 28.4 | 69.1 | 121.6 | 239.8 | 457.7 | 1289.3 |

**FIGURE 5-10.** Incidence of hip fracture (per 100,000) in 1990 by age, sex, and region. (*Adapted from* Gullberg *et al.* [17].)

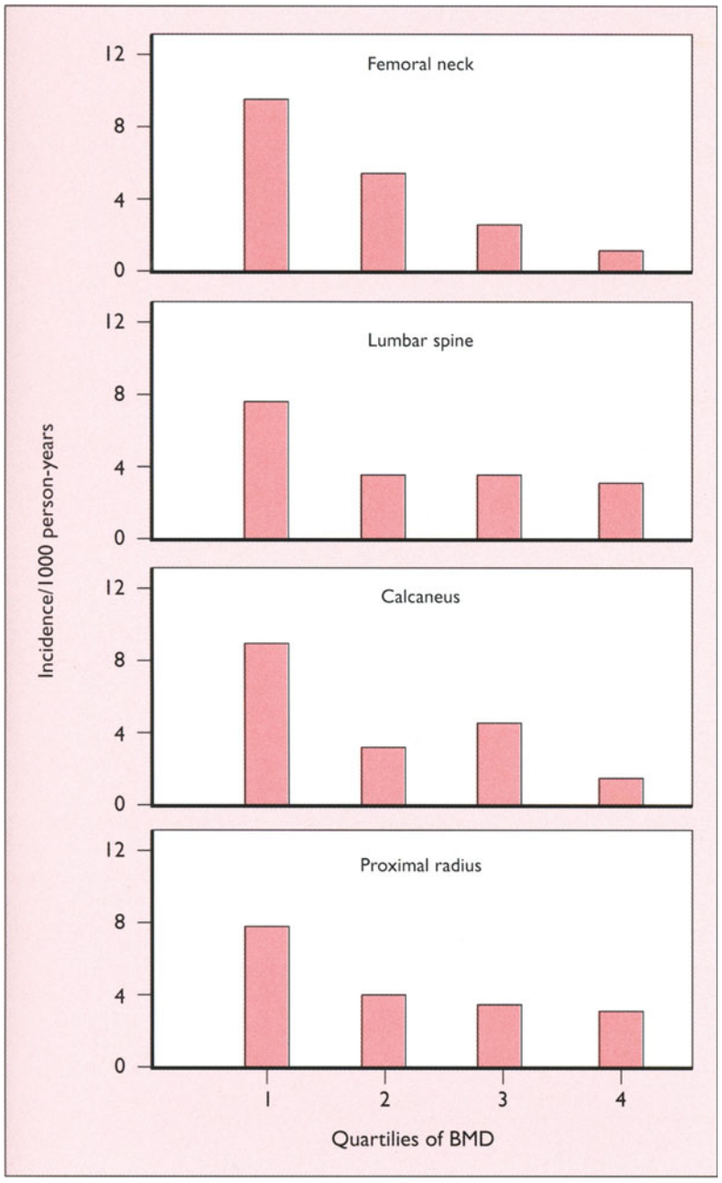



**FIGURE 5-11.** Incidence of hip fracture by age-adjusted quartile of bone mineral density (BMD). Bone mineral density measured in any of the regions of the proximal femur is more strongly associated with the subsequent risk of hip fracture than BMD measured in the radius, calcaneus, or spine. An older woman in the lowest quartile of femoral neck BMD had a risk of hip fracture 8.5 times greater than that of those in the highest quartile of BMD. Data based on 65 women who had hip fractures during 1.8 years of follow-up after the second annual clinic examination in the Study of Osteoporotic Fractures. (*Adapted from* Cummings *et al.* [18].)

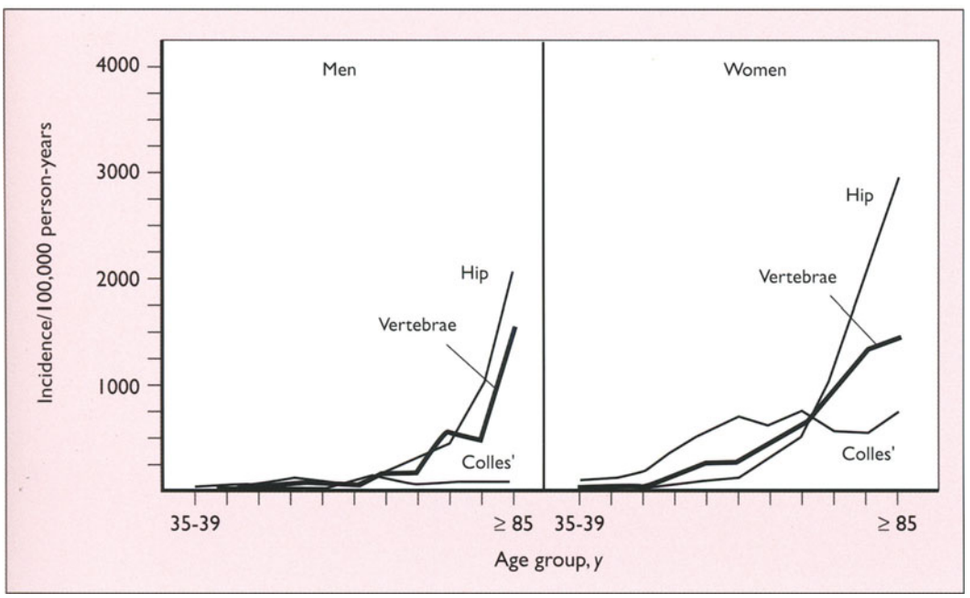



**FIGURE 5-12.** Age-specific incidence rates for hip, vertebral, and distal forearm (Colles') fractures in men and women in Rochester, Minnesota. As the population ages, there will be a dramatic increase in the number of fractures that occur, owing to the exponential relationship of fracture rate to age. (*Adapted from* Cooper and Melton [19].)

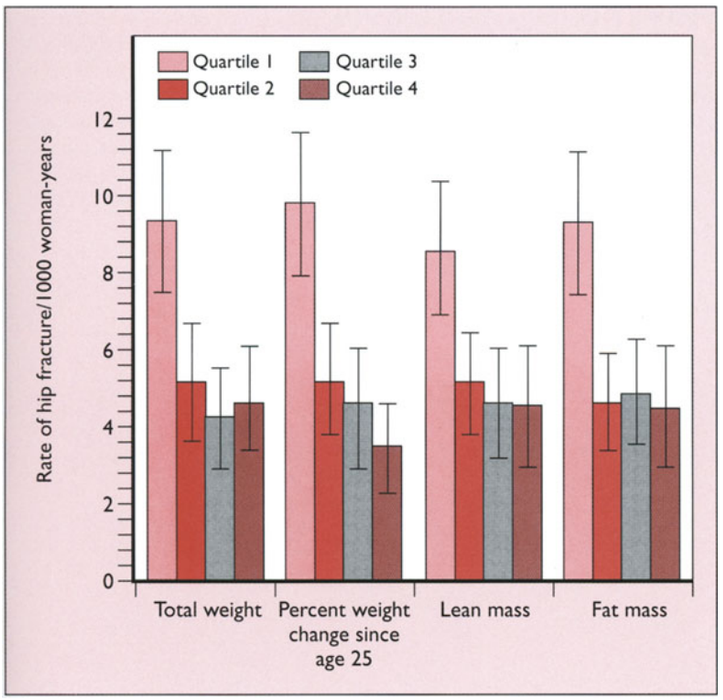



**FIGURE 5-13.** Rate of hip fracture by quartile of body size measures. Fracture rates are adjusted for age. Vertical bars denote 95% confidence intervals. Quartile cutpoints: total weight (kg): 57.8, 64.9, 73.3; percent weight since age 25 (%): 5.0, 16.4, 29.6; lean mass (kg): 36.6, 39.3, 42.4; fat mass (kg): 20.6, 25.5, 31.6. Women with smaller body size (women in the first quartile of each measurement) had a higher risk of hip fracture than women with average and larger body sizes (women in the second, third, and fourth quartiles of each measurement), who had similarly lower risks of hip fracture. Data based on 8011 ambulatory, nonblack women 65 years of age and older enrolled in the Study of Osteoporotic Fractures. (*Adapted from* Ensrud *et al.* [20].)

**OBSERVED PREVALENCE, SMOOTHED PREVALENCE, AND ESTIMATED INCIDENCE OF VERTEBRAL DEFORMITIES AMONG AN AGE-STRATIFIED RANDOM SAMPLE OF ROCHESTER, MINNESOTA, WOMEN AGED 50 YEARS AND OLDER, COUNTING ALL DEFORMITIES**

| Age, y | Sampled, *n* | Women with Deformities, *n* | Observed Prevalence (per 100) | Smoothed Prevalence (per 100)* | Estimated Incidence (per 100)† |
|---|---|---|---|---|---|
| 50–54 | 106 | 11 | 10.4 | 7.6 | 5.8 |
| 55–59 | 137 | 16 | 11.7 | 10.8 | 8.2 |
| 60–64 | 112 | 14 | 12.5 | 15.1 | 11.4 |
| 65–69 | 107 | 18 | 16.8 | 20.8 | 15.4 |
| 70–74 | 80 | 24 | 30.0 | 27.8 | 20.4 |
| 75–79 | 100 | 33 | 33.0 | 36.2 | 26.1 |
| 80–84 | 59 | 33 | 55.9 | 45.5 | 32.1 |
| 85–89 | 49 | 24 | 49.0 | 55.1 | 37.7 |
| >90 | 12 | 9 | 75.0 | 64.3 | — |
| Total | 762 | 182 | 23.9 | 25.3‡ | 17.8§ |

**Smoothed age-specific prevalence (%) of one or more vertebral deformities, as determined by the method of Leske et al. [21].*
*†Estimated age-specific incidence per 1000 person-years, as determined from smoothed prevalence rates by the method of Leske et al. [21].*
*‡Overall prevalence directly age-adjusted to the population structure of 1990 Rochester, Minnesota, women 50 years of age and older.*
*§Overall incidence directly age-adjusted to the population structure of 1990 Rochester, Minnesota, women 50 years of age and older, assuming the 85 to 89 year rate applies to the whole population aged 85 years and older.*

**FIGURE 5-14.** Observed prevalence, smoothed prevalence, and estimated incidence of vertebral deformities among an age-stratified random sample of Rochester, Minnesota, women aged 50 years and older, counting all deformities. An age-stratified sample of 762 Rochester, Minnesota, women aged 50 years and older underwent columbar radiography. Height ratios were used to characterize three types of vertebral deformity: anterior wedge deformity, concavity (or end-plate) deformity, and compression (or crush) deformity. (*Data from* Leske *et al.* [21] and Melton *et al.* [22].)

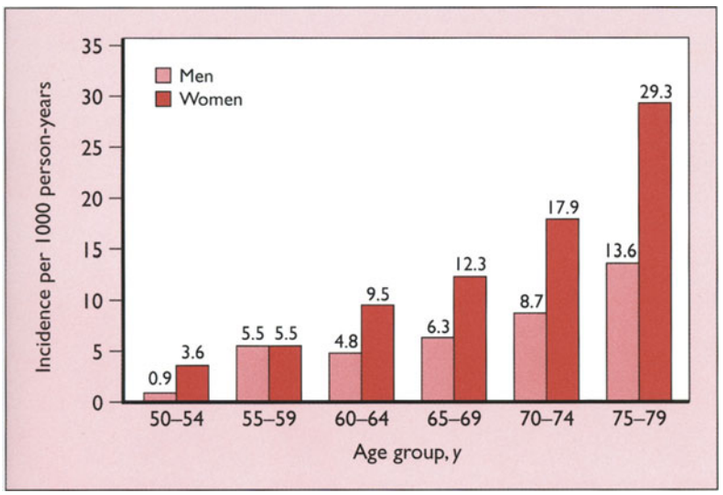



**FIGURE 5-15.** Incidence of vertebral fractures in women and men from Europe by age group. Vertebral fractures were diagnosed from lateral radiographs of the spine and defined as 20% and at least a 4-mm reduction in the measure of height in the same vertebral body. (*Adapted from* The European Prospective Osteoporosis Study [23].)

# Risk Factors for Osteoporotic Fractures

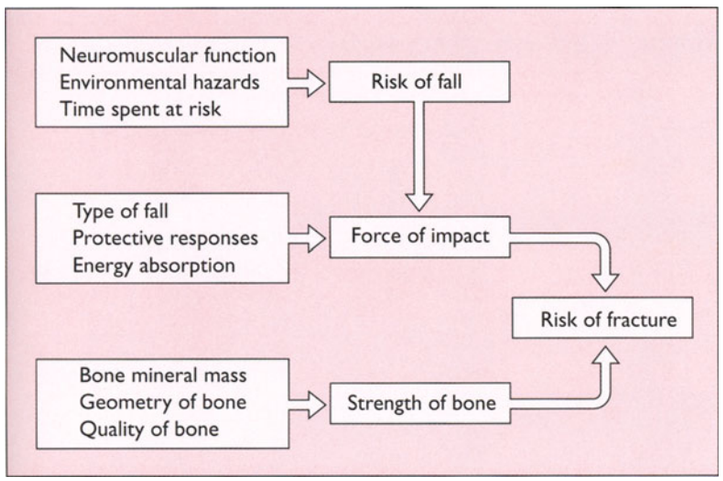



**FIGURE 5-16.** Determinants of fracture risk. (*Adapted from* Kanis and McCloskey [24].)

**RISK FACTORS FOR HIP FRACTURE IN OLDER WHITE WOMEN**

| Measurement | Approximate Increase in Hip Fracture Risk, % |
|---|---|
| Age (per 5 y) | 40 |
| History of maternal hip fracture (vs none) | 80 |
| Increase in weight since age 25 (per 20%) | -20 |
| Height at age 25 (per 6 cm) | 30 |
| Self-rated health (per 1 point decrease) | 60 |
| Previous hyperthyroidism (vs none) | 70 |
| Current use of long-acting benzodiazepines (vs no current use) | 60 |
| Current use of anticonvulsant drugs (vs no current use) | 100 |
| Current caffeine intake (per 190 mg/d) | 20 |
| Walking for exercise (vs not walking for exercise) | -30 |
| On feet ≤ 4 h/d (vs > 4 h/d) | 70 |
| Inability to rise from a chair (vs no inability) | 70 |
| Lowest quartile for distant depth perception (vs other three) | 40 |
| Low-frequency contrast sensitivity (per 1 SD decrease) | 20 |
| Resting pulse rate > 80 beats/min (vs ≤ 80 beats/min) | 70 |
| Any fracture since age 50 (vs none) | 50 |
| Calcaneal BMD (per 1 SD decrease) | 60 |

**FIGURE 5-17.** Annual risk of hip fracture according to risk factors assessed in 9516 white women 65 years of age or older who had no previous hip fracture and who were enrolled in the Study of Osteoporotic Fractures. Women were followed at 4-month intervals for an average of 4.1 years to determine the frequency of hip fracture. BMD—bone mineral density; SD—standard deviation. (*Adapted from* Cummings *et al.* [25].)

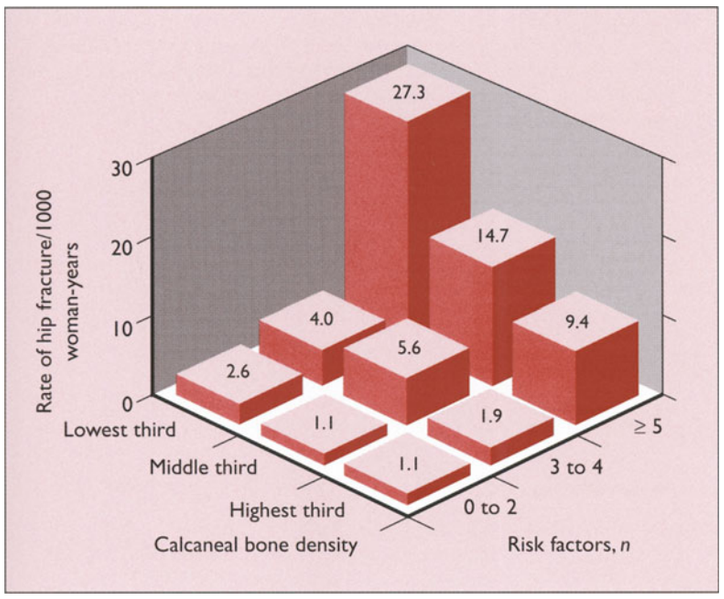



**FIGURE 5-18.** Annual risk of hip fracture according to number of risk factors and age-specific calcaneal bone density. Risk factors were assessed in 9516 white women 65 years of age or older who had no previous hip fracture and who were enrolled in the Study of Osteoporotic Fractures. Risk factors are given in Figure 5-17. Women were followed at 4-month intervals for an average of 4.1 years to determine the frequency of hip fracture. (*Adapted from* Cummings *et al.* [25].)

**RISK FACTORS FOR OSTEOPOROTIC FRACTURE IN ELDERLY MEN**

| Risk Factor | Unit | Univariate Analysis | | Adjusted for Bone Mineral Density | |
|---|---|---|---|---|---|
| | | OR | 95% CI | OR | 95% CI |
| Age | 7.7 years | 1.41 | 1.29–1.55 | 1.16 | 1.04–1.31 |
| Femoral neck BMD | 0.12 g/cm$^2$ | 0.72 | 0.63–0.82 | — | — |
| Quadriceps strength | 10 kg | 0.81 | 0.71–0.91 | 0.88 | 0.75–0.99 |
| Body sway | 515 mm$^2$ | 1.16 | 1.04–1.29 | 1.13 | 1.01–1.27 |
| Previous falls | Yes/no | 1.10 | 1.0–1.29 | 1.19 | 1.07–1.33 |
| Previous fractures | Yes/no | 1.19 | 1.10–1.30 | 1.35 | 1.23–1.50 |
| Weight | 12.7 kg | 0.81 | 0.72–0.92 | 0.90 | 0.79–1.04 |
| Height | 6.9 cm | 0.81 | 0.71–0.90 | 0.87 | 0.77–0.99 |
| Alcohol use | Yes/no | 0.73 | 0.66–0.81 | 0.93 | 0.83–1.05 |
| Activity index | 7.0 | 0.71 | 0.55–0.91 | 0.86 | 0.72–1.02 |
| Thiazide use | Yes/no | 0.89 | 0.81–1.00 | 0.97 | 0.86–1.10 |

**FIGURE 5-19.** Risk factors for osteoporotic fracture in elderly men. Risk factors for total fractures as analyzed individually and adjusted for femoral neck bone mineral density (BMD) were as follows: advancing age, fracture within previous 5 years, falls within previous 12 months, higher body sway, and shorter height. Risks of atraumatic fractures in elderly men, expressed as standardized odds ratios (OR) and 95% confidence intervals (CI) for 1 standard deviation change were estimated by Cox's proportional hazards model. Data from the Dubbo Osteoporosis Epidemiology Study, Australia, 1989–1994. Adjustment for femoral BMD in height, body sway, previous falls, previous fractures, and quadriceps strength as the only significant predictors of fractures. (*Adapted from* Nguyen *et al.* [26].)

**MULTIVARIATE ANALYSIS OF RISK FACTORS FOR HIP FRACTURES IN BLACK WOMEN**

| Variable | Adjusted Odds Ratio* (95% CI) |
|---|---|
| Body mass index† | |
| ≤ 22.6 | 13.5 (4.3–43.3) |
| 22.7–24.4 | 4.2 (1.3–14.0) |
| 24.5–27.2 | 3.5 (1.2–10.3) |
| 27.3–31.5 | 1.5 (0.4–5.3) |
| ≥ 31.6 | 1.0 |
| Estrogen therapy lasting ≥ 1 y | |
| Women < 75 | 0.1 (<0.1–0.5) |
| Women ≥ 75 | 1.1 (0.2–6.3) |
| Alcohol consumed past year (drinks/week‡) | |
| ≤ 1 | 1.0 |
| 2–6 | 2.0 (0.8–5.0) |
| ≥ 7 | 4.6 (1.5–4.1) |
| History of stroke (vs none) | 3.1 (1.2–8.1) |
| Use of ambulatory aids (vs none)§ | 5.6 (2.7–11.5) |
| Chronic illnesses (number)¶ | |
| 0 | 1.0 |
| 1 | 1.8 (0.9–3.7) |
| 2–6 | 0.9 (0.3–2.4) |

*Ratios based on conditional logistic regression models, with control for age category, zip code or telephone exchange, age as a continuous variable, and all other variables shown in the table.
†Expressed in quintiles based on the distribution of community controls.
‡Based on the assumption that one bottle of beer, one glass of wine, and one drink of spirits each contain 30 mL (1 oz) of alcohol.
§Includes women who used a cane, walker, wheelchair, artificial leg, or leg brace or who were confined to bed.
¶Expressed as a categorical variable and including the following six conditions: diabetes mellitus, coronary heart disease, epilepsy, kidney disease, Parkinson's disease, and cancer.

**FIGURE 5-20.** Multivariate analysis of risk factors for hip fractures in black women. CI—confidence interval. (*Adapted from* Grisso *et al.* [27].)

**OSTEOPOROSIS ATTRIBUTION PROBABILITIES BY FRACTURE TYPE, GENDER, AND AGE: WHITE POPULATION**

| | Age Group, y | | |
|---|---|---|---|
| Site | 45–64 Median Attribution Probability (Range)* | 65–84 Median Attribution Probability (Range) | ≥85 Median Attribution Probability (Range) |
| Women | | | |
| Hip | 0.80 (0.25–0.80) | 0.90 (0.80–0.95) | 0.95 (0.90–1.0) |
| Spine | 0.80 (0.50–0.85) | 0.90 (0.70–0.95) | 0.95 (0.80–1.0) |
| Forearm | 0.70 (0.10–0.70) | 0.70 (0.50–0.80) | 0.80 (0.70–0.95) |
| Other sites | 0.45 (0.05–0.55) | 0.50 (0.25–0.65) | 0.60 (0.45–0.80) |
| Men | | | |
| Hip | 0.60 (0.10–0.70) | 0.80 (0.60–0.95) | 0.85 (0.80–0.95) |
| Spine | 0.70 (0.50–0.90) | 0.90 (0.50–0.95) | 0.90 (0.60–0.95) |
| Forearm | 0.40 (0.05–0.50) | 0.45 (0.15–0.60) | 0.45 (0.30–0.60) |
| Other sites | 0.15 (0.05–0.30) | 0.30 (0.20–0.40) | 0.45 (0.30–0.50) |

*Probability can range from 0.00 (no attribution) to 1.00 (100% attribution).

**FIGURE 5-21.** Osteoporosis attribution probabilities by fracture type, gender, and age: white population. It is estimated that 90% of proximal femur fractures in white women aged 65 to 84 years are related to osteoporosis, whereas about 80% of hip fractures among white men are attributed to osteoporosis. The attribution probabilities were consistently less for white men than for white women. Using a three-round Delphi process [27], a panel of expert clinicians estimated the probability that each of 72 categories, consisting of four fracture types (hip, spine, forearm, all other sites combined), three age groups (45–64, 65–84, 85 years and older), three racial groups (white, black, all others [not shown]), and both genders (female, male) are associated with osteoporosis. (*Adapted from* Melton *et al.* [28].)

**OSTEOPOROSIS ATTRIBUTION PROBABILITIES BY FRACTURE TYPE, GENDER, AND AGE: BLACK POPULATION**

| Site | Age Group | | |
|---|---|---|---|
| | 45–64 Median Attribution Probability (Range)* | 65–84 Median Attribution Probability (Range) | ≥85 Median Attribution Probability (Range) |
| Women | | | |
| Hip | 0.65 (0.15–0.75) | 0.80 (0.50–0.95) | 0.95 (0.60–0.95) |
| Spine | 0.65 (0.40–0.75) | 0.80 (0.50–0.90) | 0.90 (0.60–0.95) |
| Forearm | 0.55 (0.05–0.60) | 0.60 (0.30–0.75) | 0.70 (0.40–0.85) |
| Other sites | 0.35 (0.05–0.40) | 0.40 (0.15–0.50) | 0.45 (0.20–0.70) |
| Men | | | |
| Hip | 0.30 (0.05–0.65) | 0.65 (0.10–0.85) | 0.75 (0.25–0.90) |
| Spine | 0.55 (0.30–0.80) | 0.75 (0.30–0.90) | 0.85 (0.30–0.95) |
| Forearm | 0.20 (0.05–0.40) | 0.30 (0.10–0.50) | 0.35 (0.20–0.50) |
| Other sites | 0.15 (0.05–0.20) | 0.15 (0.05–0.30) | 0.25 (0.15–0.40) |

**Probability can range from 0.00 (no attribution) to 1.00 (100% attribution).*

**FIGURE 5-22.** Osteoporosis attribution probabilities by fracture type, gender, and age: black population. It is estimated that 80% of proximal femur fractures in black women aged 65 to 84 years are related to osteoporosis, whereas about 65% of hip fractures among black men are attributed to osteoporosis. The attribution probabilities were consistently less for black than white women and men. (*Adapted from* Melton *et al.* [28].)

# Role of Falls

**ORIENTATION OF THE FALL, POINT OF IMPACT, AND RISK OF HIP FRACTURE AND WRIST FRACTURE (VS NO FRACTURE) AMONG THOSE WHO FELL**

| Variable (units) | Odds Ratio (95% Confidence Limits) for Risk of Fracture in Those Who Fell* | |
|---|---|---|
| Hip | | |
| Age (+ 5 y) | 1.3 (1.1, 1.7) | 1.4 (1.1, 1.8) |
| Walking speed (-0.23 m/s)† | 1.1 | 1.0 |
| Fall during stand/turn/transfer (0, 1 = yes) | 1.8 (1.1, 3.0) | 1.4 |
| Fall while descending steps (0, 1 = yes) | 1.1 | 0.9 |
| Fall sideways, straight down (0, 1 = yes) | | 3.3 (2.0, 5.6) |
| Fall on hip/side of leg/buttocks (0, 1 = yes) | | 32.5 (9.9, 10) |
| Wrist‡ | | |
| Age (+ 5 y) 1.0 | 1.0 | 1.1 |
| Walking speed (-0.23 m/s)† | 1.0 | 1.0 |
| Fall while walking/running (0, 1 = yes) | 1.3 | 1.4 |
| Fall backward vs sideways (0, 1 = yes) | | 2.2 (1.3, 3.8) |
| Fall forward vs sideways (0, 1 = yes) | | 0.5 (0.3, 0.8) |
| Fall on hand/wrist (0, 1 = yes) | | 20.4 (11.5, 36.0) |

**Comparison of subjects who fell and fractured a hip with those who fell without a fracture. Odds ratios are adjusted for all the other variables in each column plus calcaneus bone density. Confidence limits shown only for significant odds ratios.*

*†Odds ratios are for 1-standard deviation decrease.*

*‡Comparison of subjects who fell and fractured a wrist and those who fell without a fracture. Odds ratios are adjusted for all the other variables in each column plus distal radius bone density.*

**FIGURE 5-23.** Orientation of the fall, point of impact, and risk of hip fracture and wrist fracture (vs no fracture) among those who fell. Nonblack women aged 65 years and older living in the community who suffered hip fractures ($n$ = 130) as the result of a fall and a consecutive sample of women who fell without a fracture ($n$ = 467) were interviewed about their falls. These results are based on a case-control analysis nested in a prospective cohort study—the Study of Osteoporotic Fractures. (*Adapted from* Nevitt *et al.* [29].)

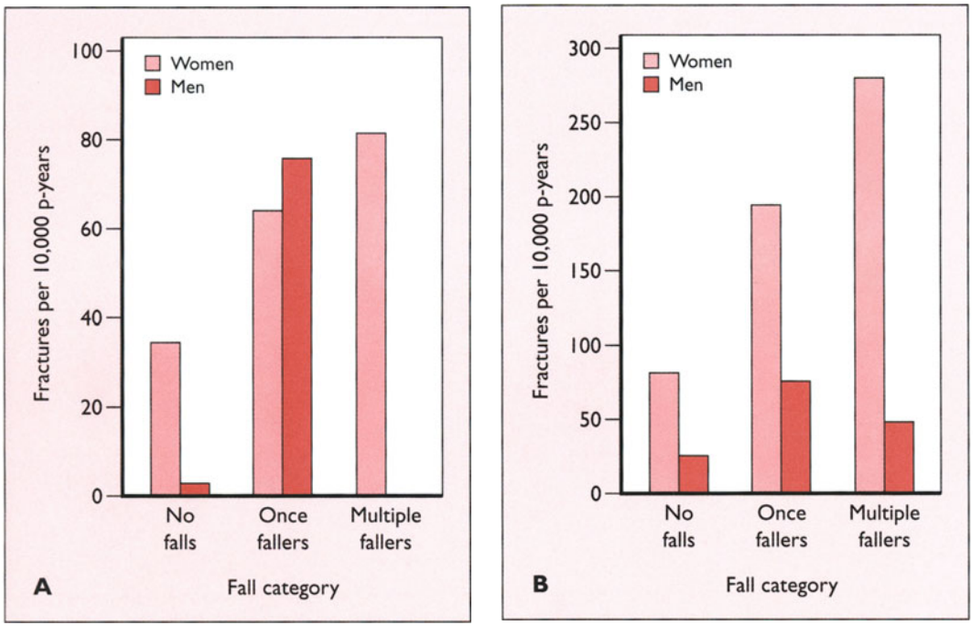



**FIGURE 5-24.** Incidence of humerus fractures (**A**) and of forearm and wrist fractures (**B**) in the previous 12 months, expressed as fractures cases per 10,000 person-years (p-years), in women (*black bars*) and men (*hatched bars*). Results classified by fall category and based on participants in the Dubbo Epidemiology Study, Australia, 1989–1997. Forty-seven percent of men ($n$ = 739 men enrolled) and 63% of women ($n$ = 1105 women enrolled) with a fracture had at least one fall. (*Adapted from* Nguyen *et al.* [30].)

# Impact of Osteoporotic Fractures: Mortality, Morbidity, and Cost

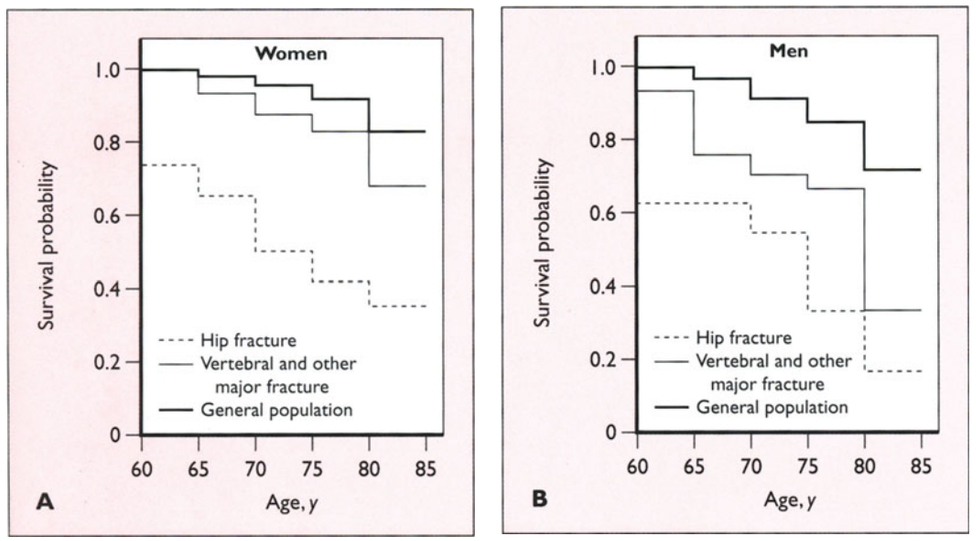



**FIGURE 5-25. A** and **B**, Cumulative survival probability by sex and type of fracture. The impact of osteoporotic fractures on survival depends on the type of fracture. Hip fractures have the greatest impact, since 10% to 20% more women die than expected for age within the first year. The risk of death is greatest immediately after fracture and declines over time. (*Adapted from* Center *et al.* [31].)

**HEALTH CARE EXPENDITURES ATTRIBUTABLE TO OSTEOPOROTIC FRACTURES IN THE UNITED STATES, BY TYPE OF SERVICE, AGE, RACE, AND TYPE OF FRACTURE, 1995**

| Covariates | Expenditure for Women (in Millions) | % of Total | Expenditure for Men (in Millions) | % of Total | Total Expenditure (in Millions) | % of Total |
|---|---|---|---|---|---|---|
| Hospital | 6805 | 49.4 | 1788 | 13.0 | 8594 | 62.4 |
| Nursing home | 3252 | 23.6 | 623 | 4.5 | 3875 | 28.2 |
| Outpatient | 1007 | 7/3 | 289 | 2.1 | 1296 | 9.4 |
| 45–64 y | 1134 | 8.2 | 569 | 4.1 | 1704 | 12.4 |
| 65–84 y | 5896 | 42.8 | 1376 | 10.0 | 7271 | 52.8 |
| 85+ y | 4034 | 29.3 | 755 | 5.5 | 4789 | 34.8 |
| White | 10,338 | 75.1 | 2526 | 18.4 | 12,863 | 93.5 |
| Nonwhite | 727 | 5.3 | 174 | 1.3 | 901 | 6.5 |
| Hip | 6720 | 48.8 | 1962 | 14.3 | 8682 | 63.1 |
| Other sites | 4345 | 31.6 | 737 | 5.4 | 5082 | 36.9 |
| Total | 11,065 | 80.4 | 2700 | 19.6 | 13,764 | 100.0 |

**FIGURE 5-26.** Health care expenditures attributable to osteoporotic fractures in the United States, 1995. In 1995, health care expenditures attributable to osteoporotic fractures were estimated at $13.76 billion, of which $10.34 billion (75.1%) was for the treatment of white women, $2.53 billion (18.4%) was for the treatment of white men, $0.73 billion (5.3%) was for the treatment of nonwhite women, and $0.17 billion (1.3%) was for the treatment of nonwhite men. (*Adapted from* Ray *et al.* [32].)

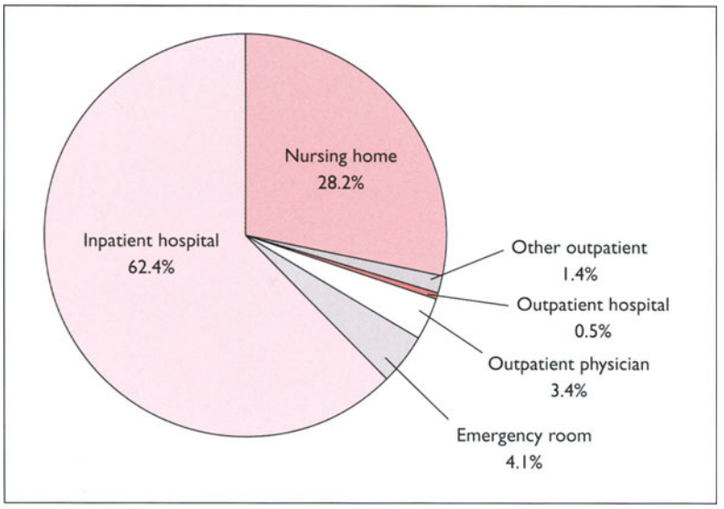



**FIGURE 5-27.** Health care expenditures attributable to osteoporotic fracture in the United States by type of service, 1995. Other outpatient includes home health care, ambulance services, and medical equipment. (*Data from* Ray *et al.* [32].)

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# 6

# *Radiology of Osteoporotic Fracture*

*Adrian J. Splitthoff, Jan E. Vandevenne, Carl S. Winalski and Philipp K. Lang*

Osteoporosis is characterized by a decrease in bone mineral density of structurally normal bone: the dynamic equilibrium between bone resorption and bone formation is perturbed in favor of bone resorption, resulting in osteopenia. Decreased bone mineral density undermines the structural integrity of bone. Quantitative bone densitometry may predict fracture risk [1]. The elastic range of osteopenic bone is decreased, and deformative stress on these bones more readily results in microfractures. Continued and progressive stress on osteoporotic bone may lead to structural failure [2,3]. For this reason, insufficiency fractures as well as fractures after minor trauma occur more frequently in the osteopenic skeleton of the patient suffering from osteoporosis. Osteoporotic fractures are seen mainly in older white women, but osteoporosis induced by any other condition, *eg,* hyperparathyroidism, cortisone treatment, and pregnancy, can lead to fractures [4]. Healing of osteoporotic fractures may be slow and difficult, and nonunion of fractures can result.

Insufficiency fractures due to osteoporosis and fractures from minor traumatic events tend to involve certain locations of the axial and appendicular skeleton. Typically, the thoracic and lumbar vertebrae and the hip, wrist, and proximal humerus are the areas involved. Thoracic and lumbar vertebrae may show collapse, and spontaneous fractures frequently occur in the pelvic girdle, especially in the sacral wings, the pubic symphysis, and the supra-acetabular region [5]. Femoral neck insufficiency fractures may occur spontaneously but are more often related to trauma. A fall on the outstretched hand is the most frequent cause of fracture of the distal radius and the proximal humerus. Less frequently, osteoporotic fractures are seen in the calcaneus, talus, proximal tibia, and ribs. This chapter provides an overview of osteoporotic fractures and their characteristic locations.

## Vertebral Compression Fractures

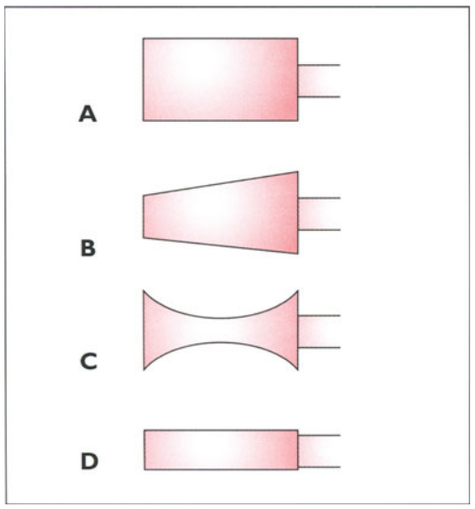



**FIGURE 6-1.** Vertebral deformity after vertebral fracture can be classified into three groups. Normal vertebrae have parallel endplates (**A**). On the lateral view, most collapsed vertebrae are wedge-shaped or biconcave. Wedge-shaped deformity is most frequently seen in thoracic vertebrae that sustain more compression anteriorly than posteriorly (**B**). Biconcave, or "fish," vertebrae have concave depressions of the upper and, sometimes also, the lower endplates and are more common in the lumbar spine (**C**). The completely collapsed vertebra demonstrates a flattened or "pancake appearance" (**D**).

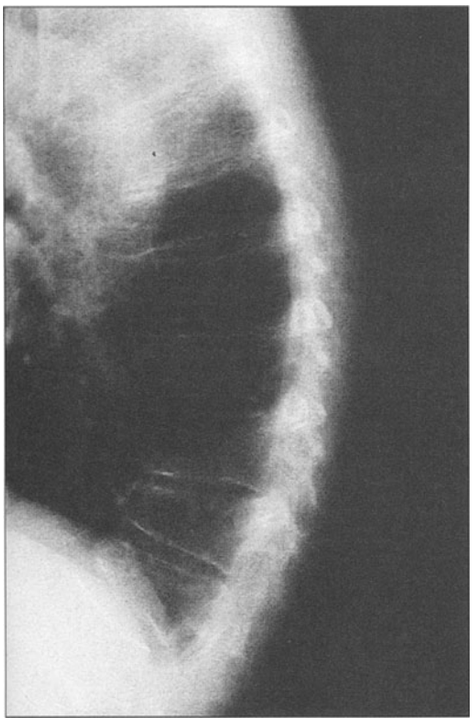


**FIGURE 6-2.** Two compression fractures of the vertebrae in the lower thoracic and upper lumbar spine as seen on the lateral chest view in a 91-year-old woman. General osteopenia of the spine is evident, with decreased density of the vertebrae and thinning of the cortical and subchondral bone. In some cases of early osteopenia, the relatively more pronounced decrease in density of the trabecular bone compared with the cortical and subchondral bone may give the erroneous impression of increased bone density in the cortical and subchondral bone. In this patient, weight-bearing forces have overmatched the structural integrity of the osteopenic vertebral bodies at the thoraco-lumbar level of the spine, which resulted in anterior collapse of the twelfth thoracic and the first lumbar vertebral body, showing a wedge-shaped deformity in these vertebrae. Vertebral collapse is frequently seen at the point of transition between the thoracic kyphosis and the lumbar lordosis.

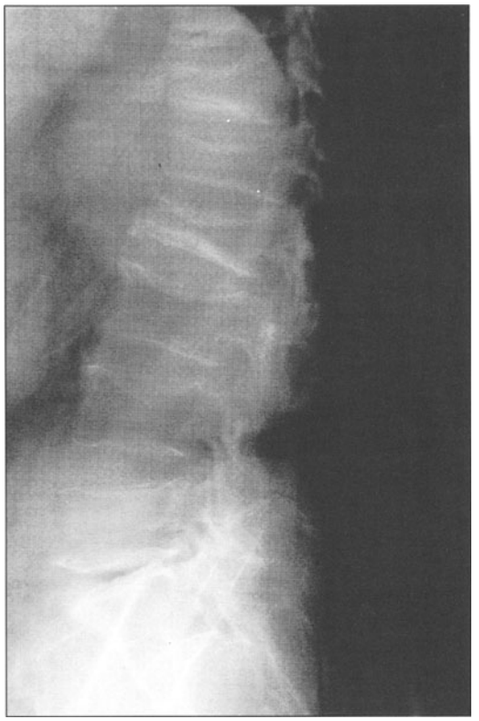


**FIGURE 6-3.** Multiple compression fractures of the lumbar spine in a 55-year-old man who received prolonged cortisone treatment. Decreased density of the vertebrae results from drug-induced demineralization of the vertebrae. Compression fractures with decreased vertebral height are seen in the twelfth thoracic vertebra, and the first, second, and third lumbar vertebrae. Biconcave collapse of the fourth lumbar vertebra is seen. Note that the disk spaces are not narrowed and even appear to be enlarged, owing to the collapse of the vertebrae. Prolonged cortisone treatment may induce pronounced osteopenia and lead to multiple compression fractures of the spine.

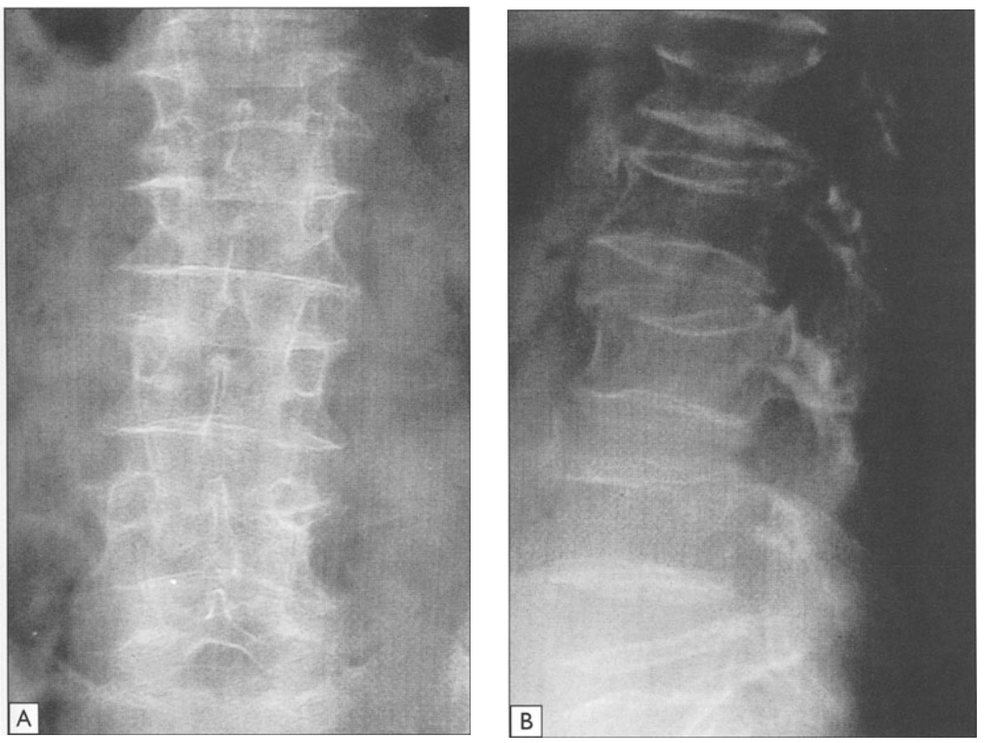



**FIGURE 6-4.** Multiple compression fractures, as seen on the anteroposterior (**A**) and lateral (**B**) views of the lumbar spine in a 76-year-old woman. Note generalized osteopenia with increased translucency of the vertebral bodies and thinning of the cortical and subchondral bone. Vertebral collapse has occurred at multiple levels. Severe compression of the fifth lumbar vertebra has resulted in a flattened vertebra. Partial collapse with loss of height and biconcave deformity is seen in the twelfth thoracic and the first three lumbar vertebrae. The height of the fourth lumbar vertebra is unchanged.

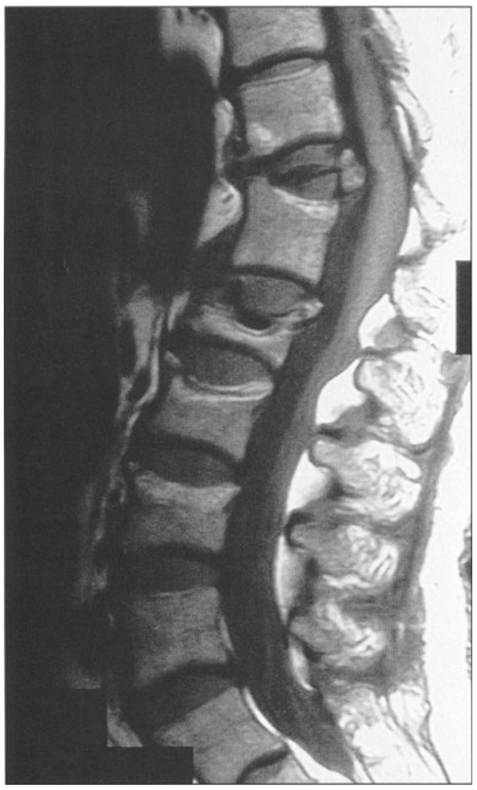
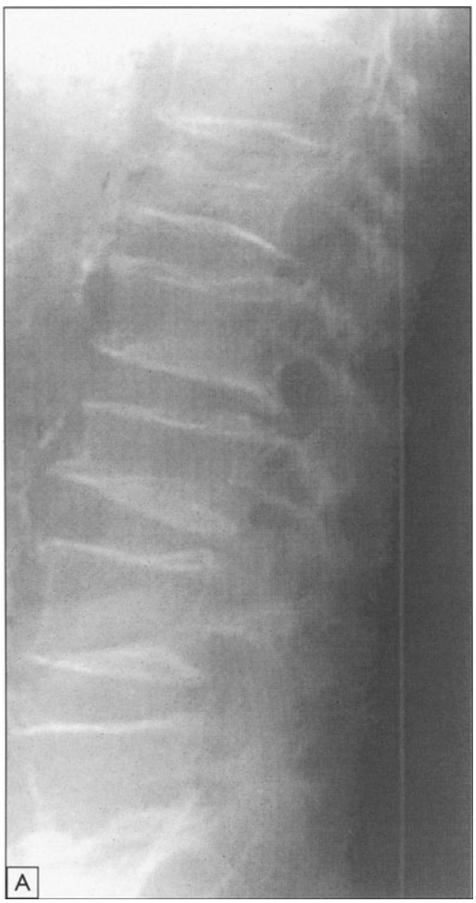


**FIGURE 6-5.** Magnetic resonance (MR) imaging of compression fractures in the spine is useful in demonstrating compression of important structures, such as spinal nerves and the spinal cord. MR imaging is also used to exclude other causes of back pain, and may help to differentiate osteoporotic compression fractures from pathologic fractures. This T1-weighted MR image was obtained after intravenous injection of gadolinium-DTPA, an MR imaging contrast agent, in a 48-year-old woman. It confirms the presence of a concave compression fracture of the upper endplate of the first lumbar vertebra. A bone fragment is seen to extend posteriorly into the epidural space. The T12 vertebral body is completely collapsed, demonstrating low signal intensity on this sequence. There is a second, larger bone fragment in the epidural space posteriorly at this level. Also seen is depression of the superior endplates of the second and third lumbar vertebrae. The spinal cord compression by the collapsed vertebral bodies represents clinically important information in this patient.

MR imaging can be used to exclude the presence of a neoplastic process as the underlying cause of compression fractures, *eg,* by absence of a mass lesion. Specific sequences or injection of gadolinium contrast agent can be used to demonstrate a neoplastic mass within the collapsed vertebra [6–9]. When malignancy is suspected for clinical reasons and MR cannot exclude a neoplastic process, biopsy should be performed.



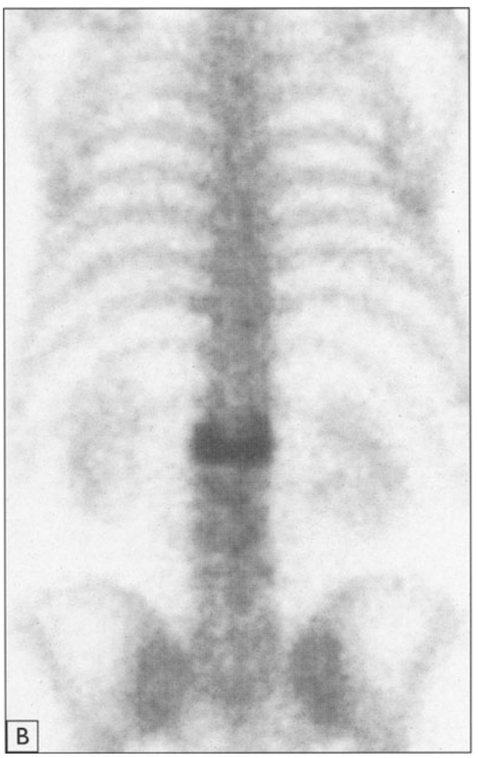




**FIGURE 6-6.** Lateral radiograph (**A**) and bone scan (**B**) of the lumbar spine in a patient with multiple compression fractures of thoracic and lumbar vertebrae. A generalized decrease in bone density is noted as well, which represents bone demineralization and thinning of the bony trabeculae and the cortical bone. The lateral view of the lumbar spine shows several compression fractures, whereas the bone scan is positive in only the L1 vertebral body. This finding suggests an acute process in the L1 vertebral body and makes the fractures of the other vertebral bodies likely to be older ones.

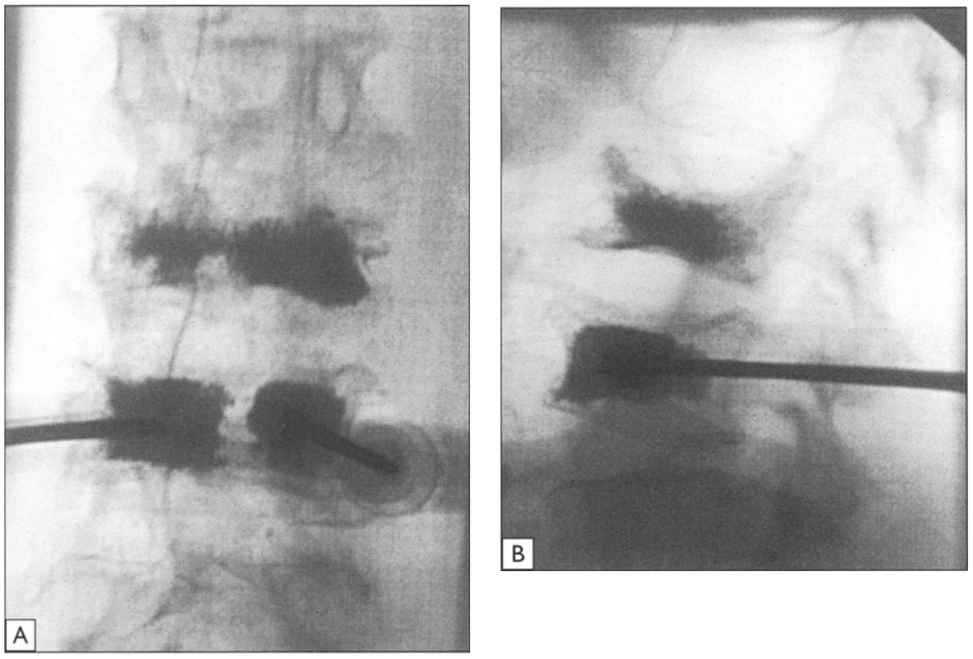



**FIGURE 6-7.** Vertebroplasty performed in a 71-year-old woman as demonstrated on the anteroposterior (**A**) and lateral (**B**) views of the lumbar spine. The radiographs show osteopenia of the lumbar spine, moderate-to-severe compression deformity of the L3 vertebral body, and a biconcave compression fracture of the L4 vertebral body. Two needles are placed in the L4 vertebral body via a bilateral transpedicle approach. Cement is injected bilaterally in order to achieve an even distribution of the material in the vertebral body. The vertebroplasty of the L3 vertebral body has already been completed.

Percutaneous vertebroplasty [10–15] is a therapeutic procedure in which polymethylmethacrylate is injected under continuous radiologic guidance into a diseased vertebra. The aim of this procedure in osteoporotic vertebral lesions is to stabilize the vertebra in order to relieve pain and to prevent further deterioration of the vertebra in a patient whose pain and clinical symptoms are not responding to conservative treatment.

## Hip Fractures

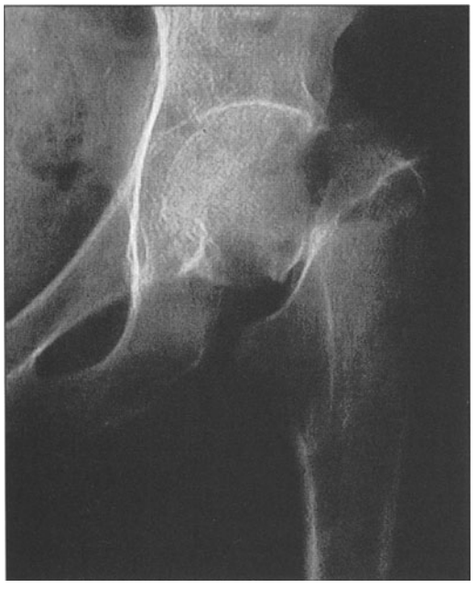


**FIGURE 6-8.** Femoral neck fracture of the left hip in a 66-year-old woman. Note the presence of a fracture of the femoral neck at the transition between the neck and the femoral head. The distal fracture fragment (femoral shaft) is displaced in a superior direction and rotated externally. Overall decreased density of the hip is indicative of osteopenia. In the normal hip, specifically arranged groups of bony trabeculae, vertically directed (compressive) and horizontally directed (tensile) groups, run through the obliquely oriented femoral neck and connect the femoral shaft with the femoral head. Bone demineralization secondary to osteoporosis decreases the loading capacity of the obliquely oriented femoral neck; as a result, fractures may occur after minor trauma. In this patient, a fall with the leg externally rotated caused the femoral neck fracture. Fractures that occur as a consequence of osteopenia in patients suffering from osteoporosis are most frequently seen in the spine, followed by the hip (proximal portion of the femur). However, hip fractures are clinically more significant and may lead to permanent disability or death, *eg,* from pulmonary embolism.

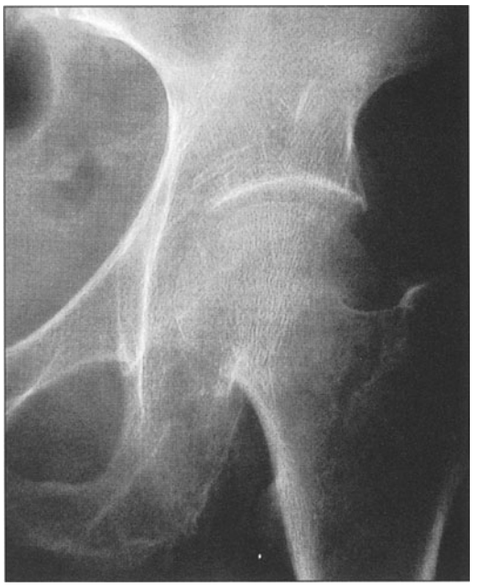


**FIGURE 6-9.** Cervical fracture of the left hip in a 73-year-old woman. Note the decreased bone mineral density in the hip and the pelvic bones. No definite fracture line can be seen, and no displacement of fracture fragments is present. However, the foreshortening of the femoral neck and the presence of a linear area of increased density perpendicular to the normal direction of the bone trabeculae indicate an impaction fracture. Classification of hip fractures by anatomic location includes subcapital, cervical, basicervical, intertrochanteric, and subtrochanteric types. Intracapsular fractures (subcapital and cervical fractures) are often classified according to the degree of displacement, as described in the Garden system [16]. Type I fractures are incomplete or impacted in nature; type II fractures are complete without osseous displacement; type III fractures are complete with partial displacement of the fracture fragments; and type IV fractures are complete with total displacement of the fracture fragments. Intracapsular hip fractures with displacement of the fracture fragments often cause avascular necrosis of the femoral head because the disrupted capsule contains the most important vessels that supply blood to the femoral head. The cervical fracture in this patient was classified as a type I according to the Garden system.

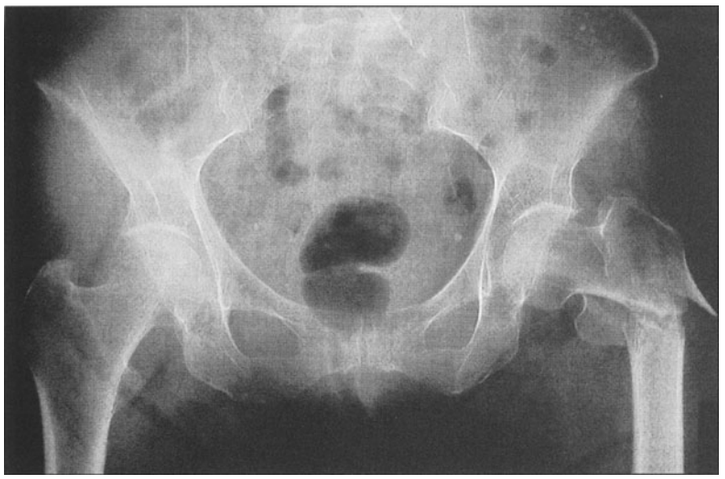


**FIGURE 6-10.** Combined subtrochanteric and intertrochanteric fracture of the left hip in a 74-year-old woman after a fall. A transverse fracture line is present inferior to the lesser and the greater trochanter, which both have been avulsed. Note varus position of the proximal fracture fragment (femoral neck) and proximal shift of the distal fracture fragment (femoral shaft). Generalized osteopenia is seen in all pelvic bones, related to osteoporosis.

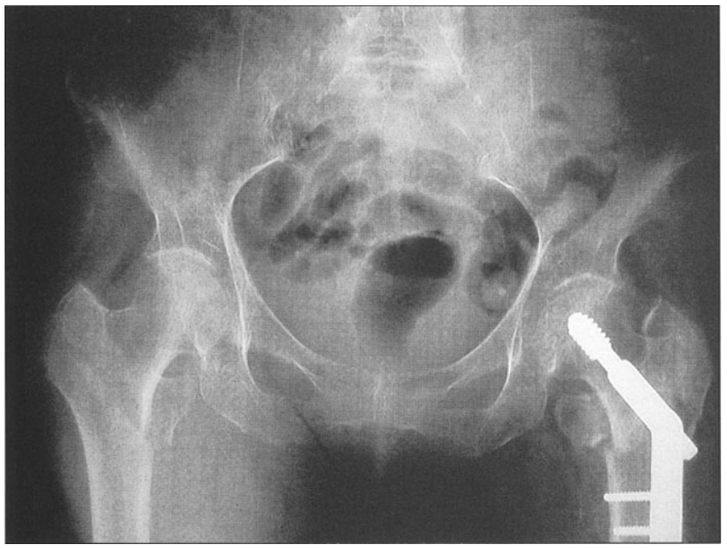


**FIGURE 6-11.** Intertrochanteric fracture of the right hip in the same patient as in Figure 6-9, 6 weeks later. Note the presence of a complete fracture through the lesser and the greater trochanters of the right hip without displacement of the fracture fragments. The fracture of the left hip has been treated surgically using a dynamic hip screw and plate device to fixate the femoral neck to the femoral shaft. Three weeks after release from the hospital, the patient fell again and fractured the right hip. Elderly patients tend to fall more often for a variety of reasons, which can contribute substantially to their increased incidence of hip fractures.

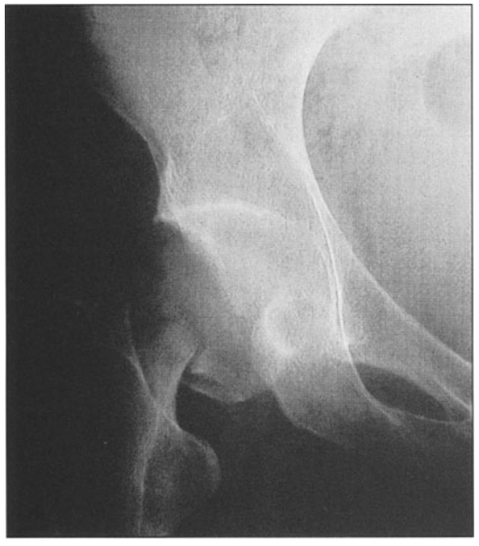


**FIGURE 6-12.** Subcapital fracture of the right hip in a patient, a few weeks after delivery of her second child. Thinning and obscuration of the subchondral cortex and decreased density of the bony trabeculae in the femoral head suggest extensive bone demineralization in the femoral head, whereas bone mineralization remains normal in the adjacent acetabulum. This radiologic image in a young woman in the postpartum period strongly suggests presence of "transient osteoporosis of the hip." Although this does not usually lead to fracture, it has resulted in a subcapital fracture in this patient. The cause of pregnancy-related transient osteoporosis is unknown, and other joints and bones may be affected [ 17,18 ]. Pregnancy-related osteoporotic fractures are rare, but they may be seen in the hip and the thoracic spine. Transient osteoporosis of the hip occurs in young and middle-aged adults and more frequently in men. It starts with spontaneous hip pain, without previous trauma, that progresses in a few weeks and usually subsides in 2 to 6 months. Radiographically progressive marked osteoporosis of the femoral head is seen several weeks after the onset of the hip pain, and restoration of the normal bone density follows clinical recovery. Magnetic resonance (MR) imaging is currently the most sensitive technique for early detection of the bone marrow edema that may indicate transient osteoporosis of the hip: extensive diffuse increased signal intensity of the femoral neck and head is seen on fat-suppressed T2-weighted MR images.

# Pelvic Insufficiency Fractures

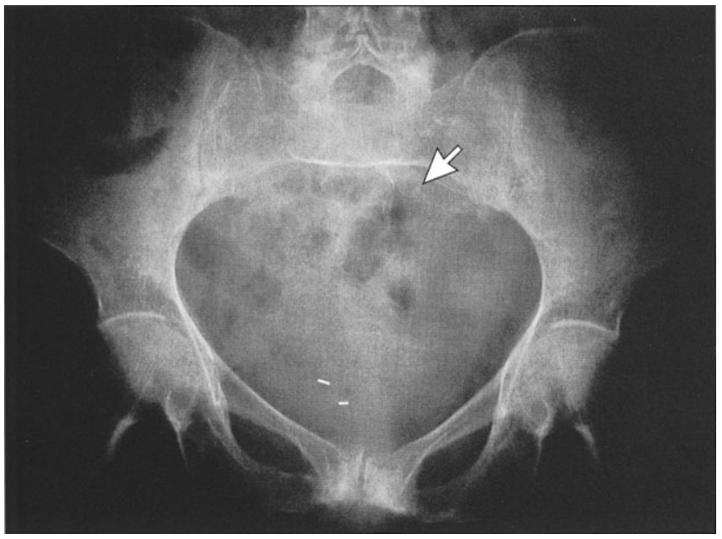


**FIGURE 6-13.** Pelvic insufficiency fractures in a 72-year-old woman. Note the overall osteopenic aspect of the pelvic bones. The pubic bones have a mixed osteosclerotic and osteolytic appearance, with irregular areas of increased and decreased density seen in the trabecular bone. The cortical bone at the symphysis is not well defined. This is indicative of insufficiency fracture of the symphysis pubis. Bilateral areas of mixed osteosclerosis and osteolysis are typically seen in insufficiency fractures of the symphysis pubis and may represent areas of microfractures and areas of bone regrowth. In some cases, bone tumors, such as chondrosarcoma, can mimic this radiologic presentation, in particular when the pathology is unilateral [19,20]. The sacrum appears very osteopenic, and the arcuate lines (*arrow*) outlining the sacral neuroforamina are indistinct. This radiologic appearance, together with the patient's clinical complaints of pain posteriorly at the pelvic girdle, raises the suspicion of sacral pathology, *eg*, sacral insufficiency fracture (see Fig. 6-14). Additionally, a step-off is noted at the inferior aspect of the left sacrum adjacent to the sacroiliac joint.

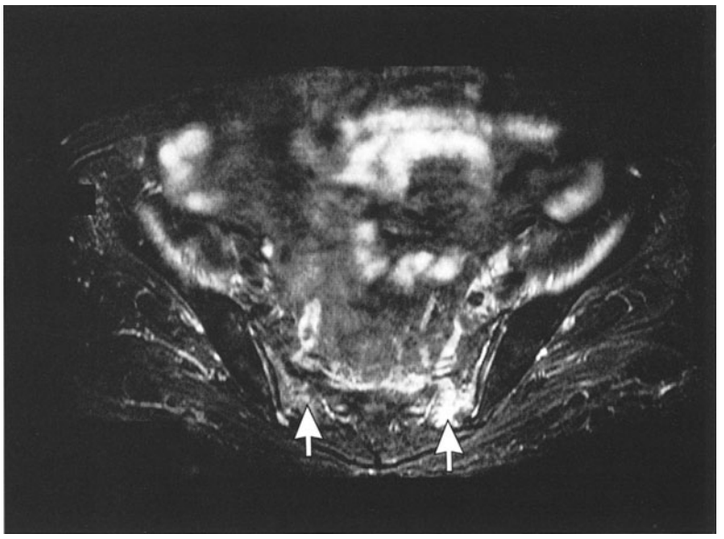


**FIGURE 6-14.** Magnetic resonance (MR) imaging of sacral insufficiency fracture in the same patient as shown in Figure 6-13. In this axial fat-saturated T2-weighted MR image, all structures with high water content have a bright signal. For example, the small intestines superiorly in the image are filled with fluid and have a bright (white) signal. Note the normal low signal (black) of the bone marrow in the iliac bones. However, increased signal (white) is seen in the sacrum bilaterally (*arrows*), which indicates increased water content of the bone marrow (*bottom center of image*). This pattern of bone marrow edema in elderly osteopenic patients is highly suggestive of bilateral sacral insufficiency fractures [21]. Bone tumors and metastases can simulate this condition, but tend to be unilateral and asymmetric, while the bone marrow edema of insufficiency fractures is usually bilateral and decreases with adequate treatment. Also, a fracture line with low signal intensity on both T1- and T2-weighted images may be visualized.

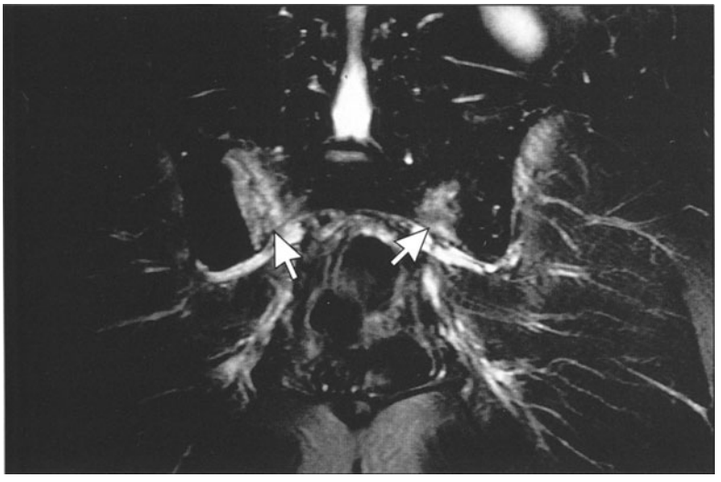


**FIGURE 6-15.** Coronal T2-weighted magnetic resonance (MR) image of insufficiency fracture of the sacrum in a 67-year-old woman. This patient was previously treated with radiotherapy for ovarian carcinoma. No metastatic lesions were diagnosed at the time of treatment. Recently, the patient complained of pain at the sacrum, and bone metastasis of ovarian carcinoma was suspected on clinical grounds. The MR examination, however, demonstrates the presence of bilateral sacral insufficiency fractures. The bone marrow edema associated with sacral insufficiency fractures is characterized by increased (white) signal (*arrows*) in the normal dark bone marrow of the sacral wings on fat-saturated T2-weighted MR images. No definite tumoral lesion is seen. Note the thin, irregular, black line in the middle of the bone marrow edema (on the *left* in the image), which represents the fracture line.

## Wrist Fractures

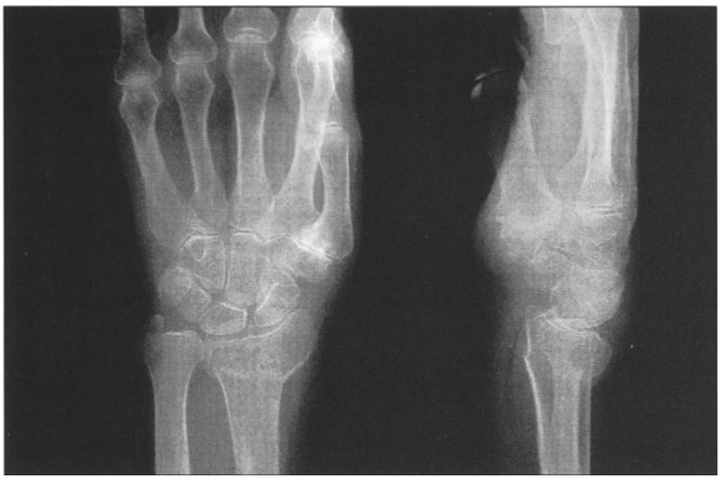


**FIGURE 6-16.** Colles' fracture as seen on the posteroanterior and lateral views of the left wrist in an 83-year-old woman. The Colles' fracture usually occurs in older individuals after a fall on the outstretched hand. Note the decreased bone mineralization. Clinically, a characteristic "dinner fork" or "bayonet" deformity is seen, owing to the dorsal angulation and shift of the distal fracture fragment and wrist. The fracture of the distal radius and the dorsal angulation are confirmed on the conventional radiographs. Additional findings commonly may include impaction and displacement of the fracture fragments of the radius and avulsion of the styloid process of the ulna. In this patient, widening of the normal space between the lunate and the scaphoid may represent scapholunar dissociation caused by axial stress of the capitate at this articulation at the time of trauma. Treatment of uncomplicated Colles' fractures consists mainly of (closed) reduction of the fracture fragments to reestablish the normal volar tilt of the radial articular surface and stabilization of the fracture fragments by casting. Note extensive osteoarthritic changes at the first carpometacarpal joint.

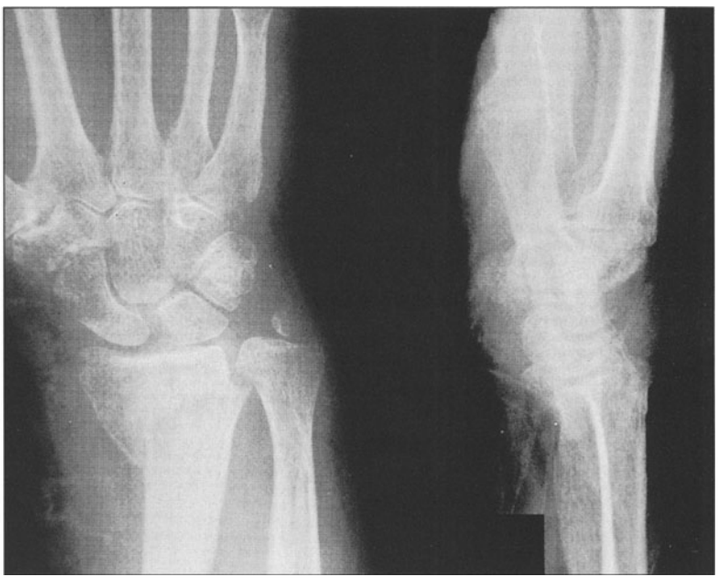


**FIGURE 6-17.** Smith's fracture of the wrist in an 84-year-old woman. On the posteroanterior view on the left, a fracture of the distal radius is seen. Volar angulation or displacement is characteristic of Smith's fracture, as seen on the right. Smith's fracture is much less common than Colles' fracture and is called Barton's fracture when the fracture involves the articular surface of the distal radius. Smith's fracture may result from a (backward) fall on the wrist in dorsiflexion with the forearm supinated. Note the concomitant avulsion of the styloid process of the ulna and the osteoarthritic changes at the first carpometacarpal joint.

## Fractures of the Proximal Humerus

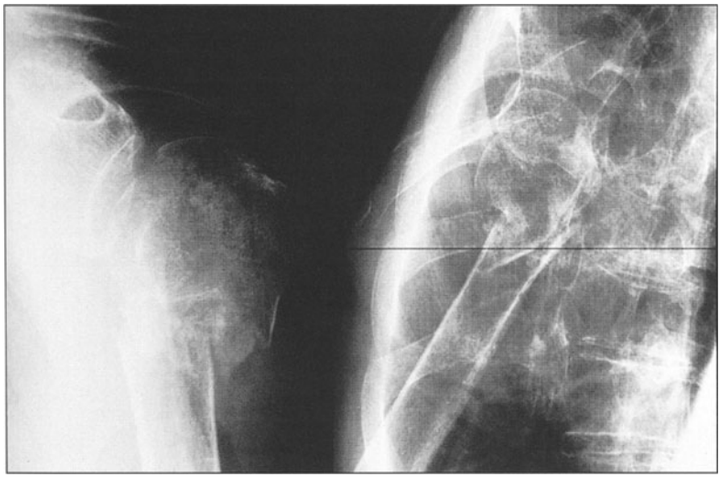


**FIGURE 6-18.** Fracture of the left proximal humerus in a 66-year-old man, as seen on the anteroposterior view (*left*) and on the transthoracic view (*right*). Note the overall decreased bone mineralization. A fracture is present at the level of the surgical neck of the humerus. The humeral head is well centered over the glenoid (see transthoracic view) and is therefore not dislocated. The distal fracture fragment (humeral shaft) is displaced anteriorly and medially as a result of traction of the pectoralis major muscle. Fracture of the greater or lesser tuberosities are not seen, and the fracture of this patient may be classified as a two-part fracture of the proximal humerus according to the Neer classification [16]. Rotator cuff tears may be associated with fractures of the greater tuberosity. Fractures of the proximal humerus in patients having osteoporosis are less common than vertebral, hip, and wrist fractures and most often result from a fall on the outstretched hand. Closed and rarely open reduction of the fracture may sometimes be required.

# Other Insufficiency Fractures

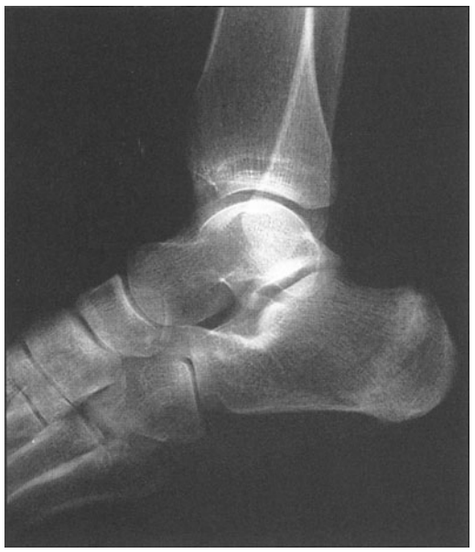


**FIGURE 6-19.** Insufficiency fracture of the right calcaneus in a 62-year-old woman. A linear area of radiodensity in the posterior part of the calcaneus is present, and aligned perpendicular to the direction of the bony trabeculae. This represents bone sclerosis and healing of a cancellous bone insufficiency fracture of the calcaneus. Calcaneal stress fractures may also be seen in healthy runners or in patients with diabetes. Decreased bone mineralization, as in patients with osteoporosis, results in a decreased elastic capacity of the bones and microfractures occur more easily. Although these fractures occur less frequently in patients with osteoporosis, a predilection for certain anatomic locations is known and include the posterior third of the calcaneus, the medial portion of the proximal tibia, and the third and fourth metatarsal bones [22–24]. Cancellous bone stress fractures, such as in the calcaneus, may not be visible on initial radiographs, but if a radiograph is repeated 2 weeks later a linear area of bone sclerosis is often readily visible. Early diagnosis of insufficiency fractures may be enhanced with radionuclide scanning or magnetic resonance imaging.

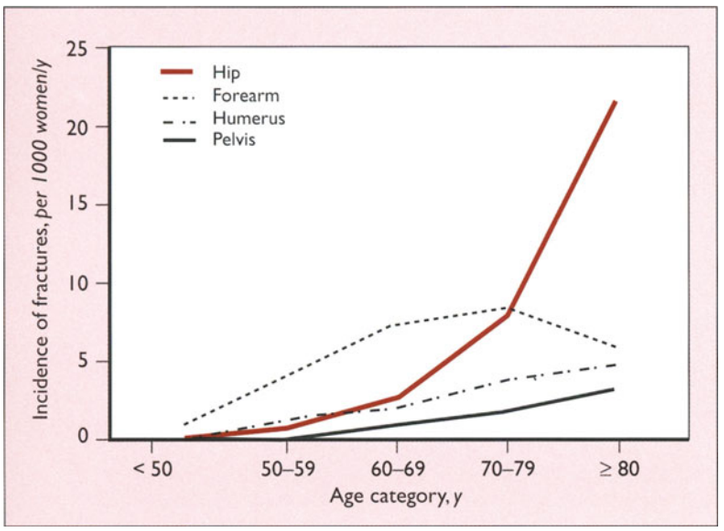



**FIGURE 6-20.** Plot showing the age-specific incidence rate of hip, forearm, humerus, and pelvic fracture per 1000 women per year in the United States [25]. The incidence of fractures in the appendicular skeleton increases with age above 50 years. Pelvic and humerus fracture incidences gradually increase to 3 and 4, respectively, per 1000 women who are 80 years of age or older. Forearm fracture incidence increases relatively quickly after the age of 50 years and reaches a plateau of 8 per 1000 women who are between the ages of 60 and 80 years old. Above the age of 80, there is a decrease in forearm fracture incidence. On the other hand, hip fractures are not frequent before the age of 60 years. After age 60 years, there is a very steep increase in hip fractures, reaching over 20 per 1000 in women older than 80 years. High mortality and morbidity is associated with hip fractures in the elderly. Maintaining body weight, walking for exercise, avoiding long-acting benzodiazepines, minimizing caffeine intake, and treating impaired visual function to prevent falls are among the steps that may decrease the risk of hip fracture in white women [26].

Most fractures after the age of 50 years are related to low bone density (osteoporosis). Other factors, such as severe trauma or specific pathologic processes (*eg,* metastatic malignancies) causing fracture, are less common. The National Osteoporosis Foundation reported on the contribution of osteoporosis to specific types of fractures among different populations residing in the United States [27]. They estimated that 90% of hip fractures in white women between 65 and 84 years old were related to osteoporosis. The estimate for spine fractures (vertebral compression fractures) was 90%, and that for wrist fractures was 70%. White women, in general, have the highest risk of osteoporotic fractures. Men are less at risk than women of the same race. Black individuals have the lowest risk, and Asians have intermediate risk.

The chance of fracture has been calculated in numerous studies and includes estimations on lifetime risk, cumulative risk, and actuarial risk. Cumulative risk is the probability that a person of an exact age (*eg,* 65 years) will sustain a fracture at a later exact age (*eg,* 90 years). The actuarial risk takes into account the chance that a person can die from another disease during this period. Therefore, actuarial risks are lower than cumulative risks. In a study using data from a 5% sample of US Medicare recipients, the actuarial risk for a 65-year-old white woman sustaining a fracture by age 90 was reported to be 16% for the hip, 9% for the distal forearm, and 5% for the proximal humerus [28]. (*Adapted from* Cummings *et al.* [25].)

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7

# LABORATORY ASSESSMENT OF SKELETAL STATUS

*Richard Eastell and Penny R. Bainbridge*

Bone turnover markers have been used in medicine for over 70 years. They have proved indispensable in the management of metabolic bone diseases such as Paget's disease of bone. The changes in bone turnover in osteoporosis are small; thus, markers that are not specific to bone were not very useful in investigating this disease. However, assays have recently been introduced that are more specific for bone. In this chapter, we consider the evidence for the use of these markers in the investigation of osteoporosis.

## Bone Turnover Markers

**MARKERS OF BONE FORMATION AND RESORPTION**

Bone formation markers (products of the osteoblast)
Serum alkaline phosphatase (bone isoform), bone alkaline phosphatase
Serum osteocalcin (OC)
Serum C- and N-propeptides of type I collagen (PICP and PINP)
Bone resorption markers (degradation products of type I collagen, enzymes)
Urinary excretion of pyridinium crosslinks of collagen, eg, deoxypyridinoline, DPD
Serum, or urinary excretion of, C- and N-telopeptides of type I collagen (CTX, NTX)
Serum, or urinary excretion of, galactosyl hydroxylysine (Gal-Hyl)
Urinary excretion of hydroxyproline (Hyp)
Serum tartrate-resistant acid phosphatase (TRACP)

**FIGURE 7-1.** There is a wide choice of biochemical turnover markers. It is usual for a laboratory to establish a marker for bone resorption, eg, urinary N-telopeptides of type I collagen, and a marker of bone formation, eg, serum bone alkaline phosphatase. These measurements are useful for the initial evaluation of the patient, for providing additional information for the prediction of rapid bone losers or fracture risk, and to stimulate the further search for secondary osteoporosis.

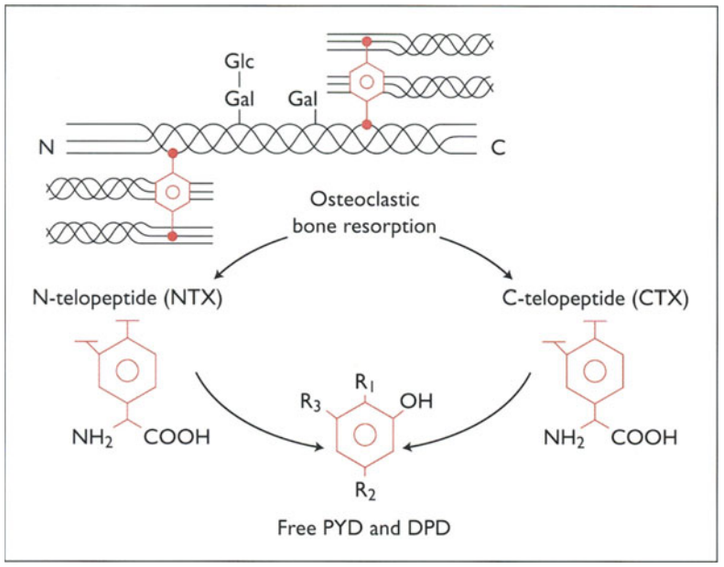



**FIGURE 7-2.** Type I collagen breakdown products as markers of bone resorption. Type I collagen is the most abundant protein in bone; the chains are held together by pyridinium crosslinks. These are released during bone resorption and are present in the serum and urine as free crosslinks (free pyridinoline [PYD] and deoxypyridinoline [DPD]) or as crosslinks bound to peptides from the N-telopeptides of type I collagen (NTX) or C-telopeptides of type I collagen (CTX) of the collagen molecule. These crosslink fractions were originally measured by high-performance liquid chromatography, but assays are now available for NTX, CTX, and free DPD in urine by immunoassay and for NTX and CTX in serum by immunoassay. Most recently, the assays for serum CTX and urinary NTX and free DPD have been established on autoanalyzer devices, which are available in most clinical chemistry laboratories. Furthermore, point-of-care devices are being developed for the measurement of these bone resorption markers in urine.

## Prediction of Bone Loss and Fractures with Bone Turnover Markers

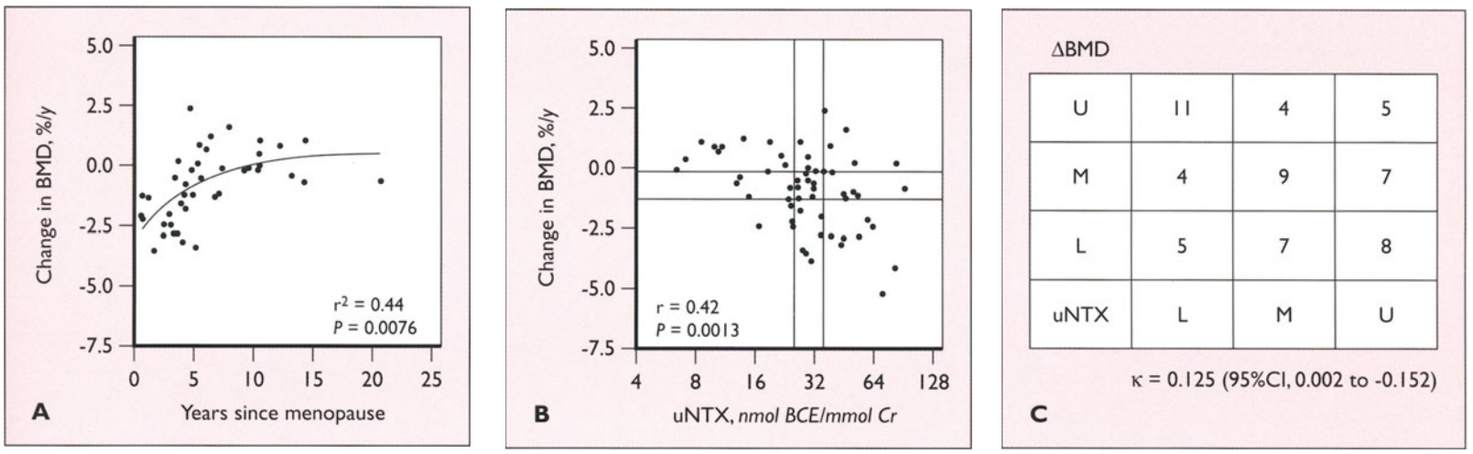



**FIGURE 7-3.** Relationship between change in bone mineral density (BMD) of the spine and bone turnover. A longstanding goal has been to use bone turnover markers to predict "fast losers" at the time of the menopause. **A,** Change in BMD after menopause. Bone loss is most rapid in the first 5 years after menopause. **B,** The higher the rate of bone resorption (measured by N-telopeptides of type I collagen [NTX] in a second morning void urine sample and expressed as a ratio to creatinine), the greater the rate of bone loss. The *broken lines* represent the boundaries between tertiles. **C,** The ability of bone resorption markers to classify individuals into upper (U), middle (M), or lower (L) tertiles of bone loss is poor (κ score of < 0.2); thus, this approach is unsuitable for use in the individual [1]. (*Adapted from* Rogers *et al.* [2].)

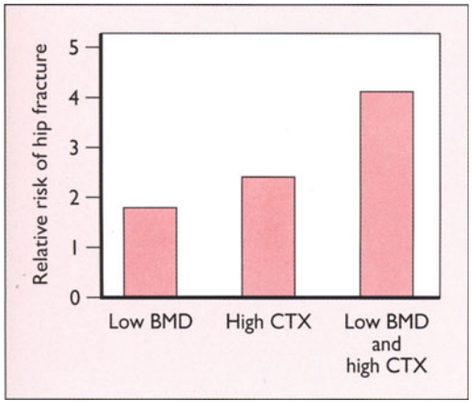



**FIGURE 7-4.** Results from the Epidimilogie de l'Osteoporose (EPIDOS) study. In older women, a high level of bone turnover has been associated with an increased risk of fracture. Results from bone turnover markers can be expressed in the same way as bone mineral density results using T scores. In this approach, a reference range is established in premenopausal women aged 30 to 50 years, with the results expressed in standard deviation units; the reference interval for young women is therefore -2 to +2. The risk of hip fracture is higher in women with low hip bone mineral density (BMD) (T< 2.9), high urinary C-telopeptides of type I collagen (CTX) (T>2), and even higher with both low bone mineral density (T<2.5) and high urinary CTX (T>2). (*Data from* Garnero *et al.* [3].)

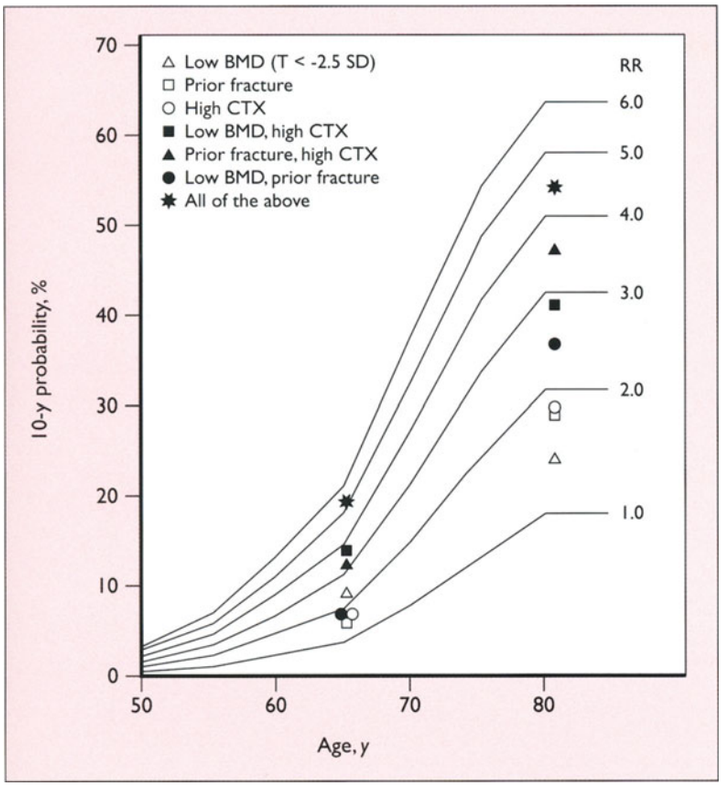



**FIGURE 7-5.** Fracture probability. The 10-year probability of a fracture increases with increasing age. The probability is further increased in the presence of low bone mineral density (BMD), a previous fracture, and high bone resorption markers (C-telopeptides of type I collagen [CTX]). The highest risk of fracture occurs in those with all three of these risk factors. (*Adapted from* Kanis *et al.* [4].)

## Monitoring the Effect of Treatment on Bone Turnover Markers

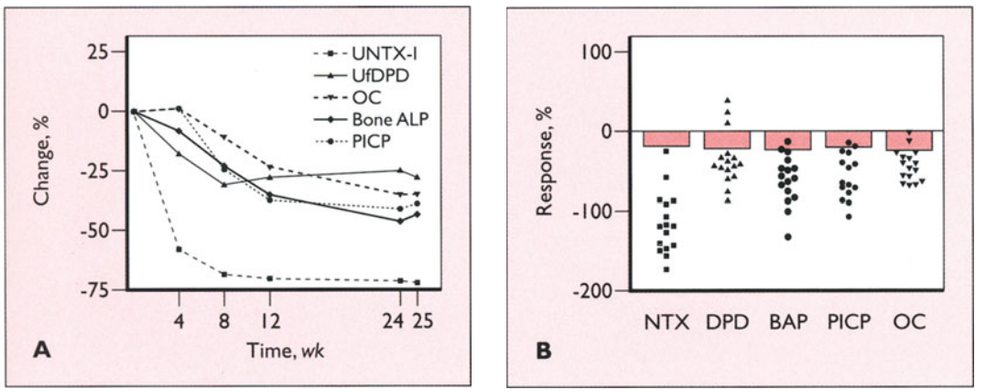



**FIGURE 7-6.** Most licensed treatments for osteoporosis work by decreasing bone turnover. This example shows the effect of alendronate therapy on bone turnover markers over 6 months. **A,** Bone resorption markers (urinary N-telopeptides of type I collagen [NTX] and urinary free deoxypyridinoline [DPD]) are suppressed within 4 to 8 weeks of starting therapy; the decrease in bone formation markers (osteocalcin [OC], bone alkaline phosphatase [BAP], C-propeptides of type I collagen [PICP]) is somewhat slower. **B,** The *boxes* show the least significant change bounds for each marker. A change in marker that exceeds the least significant change is referred to as "response." Note that most patients show a response to treatment at 6 months. Patients entering studies such as this are highly selected; in clinical practice, patients may have secondary osteoporosis that prevents them from responding to therapy, or they may not comply with instructions. (*Adapted from* Braga de Castro *et al.* [5].)

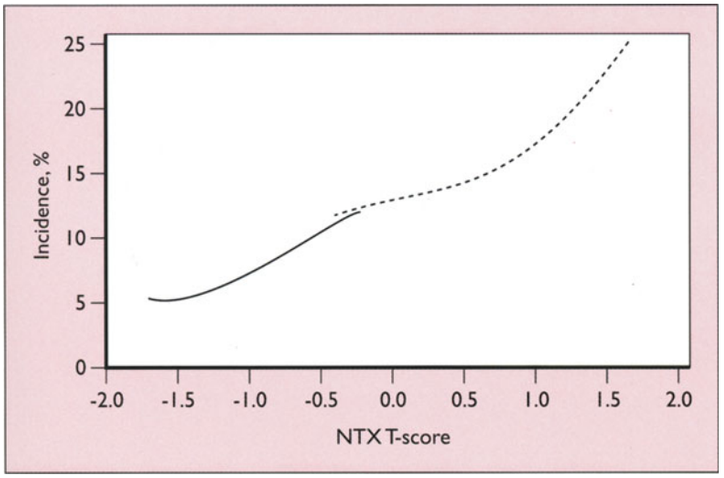



**FIGURE 7-7.** Incidence of new vertebral fractures. The incidence of new vertebral fractures is lowest in those with the lowest levels of bone resorption N-telopeptides of type I collagen (NTX) on treatment. In this study, women with vertebral fractures were treated with risedronate, 5 mg/d, for 3 years (*solid line*) or placebo (with calcium supplements; *broken line*). According to the data shown here, the optimal level of urinary NTX would be a T score of -1.5 or below (equivalent to an NTX value of < 21 nmol BCE/nmol creatinine). (*Adapted from* Eastell *et al.* [7].)

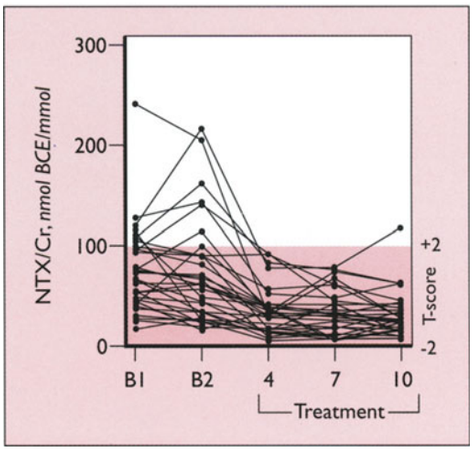



**FIGURE 7-8.** Bone resorption markers to monitor the response of the individual to antiresorptive treatments. In our practice, N-telopeptides of type I collagen (NTX) were measured in the second morning void urine sample in 49 patients with osteoporosis [8] on two occasions at baseline (B1 and B2) and then after 4, 7, and 10 months on treatment with hormone replacement therapy or bisphosphonates. Before starting treatment, the NTX level is usually within the reference interval for young women; in those with high values, the risk of fracture may be even greater, and they may be more likely to have secondary osteoporosis. Note that NTX does vary before starting treatment, which is why we make two collections and take the mean of these as our baseline. There is an early and marked decrease in NTX after starting treatment such that the maximum effect is seen by 4 months in most patients. Note that NTX is in the lower half of the premenopausal reference range (below a T score of 0) in most subjects after 10 months of treatment.

# Biochemical Evaluation of Osteoporosis: Secondary Osteoporosis

**RECOMMENDED INITIAL EVALUATION FOR OSTEOPOROSIS**

| Blood | 24-Hour Urine |
|---|---|
| Complete blood count—hemoglobin, erythrocyte sedimentation rate | Calcium |
| Calcium, phosphate | Creatinine |
| Alkaline phosphatase | |
| γ-Glutamyltranspeptidase | |
| Creatinine | |
| Thyroid-stimulating hormone | |
| Testosterone (men) | |
| Protein electrophoresis (and urinary Bence Jones protein) | |
| Parathyroid hormone | |
| Serum CTX (or urine NTX) | |
| Bone alkaline phosphatase | |

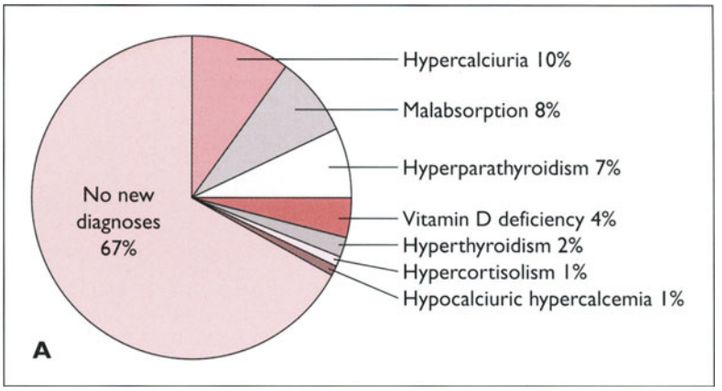
**FIGURE 7-9.** Recommended initial evaluation for osteoporosis. An underlying cause of osteoporosis may be found in about 20% of women and 40% of men with established osteoporosis. There are no guidelines on who should be evaluated, but we consider it valuable to investigate all patients presenting with vertebral fracture and all patients who have a bone mineral density value below the young adult reference range, or who have accelerated bone loss.

The choice of tests is based on our clinical experience and reports such as that shown in Figure 7-11. We usually carry out these tests in patients with osteoporosis, especially in the presence of vertebral fracture, a bone mineral density value below that expected for age ($z < -2$), and rapid bone loss. CTX—C-telopeptides of type I collagen; NTX—N-telopeptides of type I collagen.

## LABORATORY INVESTIGATION OF DISEASES IDENTIFIED BY CLINICAL EXAMINATION OR INITIAL EVALUATION

| | |
|---|---|
| Osteomalacia | Repeat serum and urinary calcium, PTH |
| | 25-Hydroxyvitamin D (25-OHD) |
| | Phosphate threshold test |
| Primary hyperparathyroidism | Repeat serum and urinary calcium and PTH |
| Malabsorption syndrome | 25-OHD |
| | Serum and urinary magnesium |
| | Antigliadin and antiendomysial antibodies |
| | Red cell folate, vitamin $B_{12}$, ferritin |
| | Repeat serum and urinary calcium |
| Hyperthyroidism | Free tri-iodothyronine ($T_3$) |
| Cushing's disease | Overnight dexamethasone suppression test |
| Hypogonadism | Sex hormone–binding globulin |
| | Luteinizing hormone |
| | Follicle-stimulating hormone |
| | Prolactin |
| Chronic renal failure | Serum calcium, phosphate |
| | 1,25-Dihydroxyvitamin D |
| Myeloma | Bone marrow biopsy |
| Hemochromatosis | Serum iron |
| | Total iron-binding capacity |
| | Ferritin |
| Primary biliary cirrhosis | Antimitochondrial antibody |
| | Immunoglobulins |
| | ALT, AST, bilirubin |
| Idiopathic hypercalciuria | Serum and urinary calcium (on low-calcium diet for 7 d), urinary sodium, serum uric acid |
| | Fasting urinary calcium and creatinine, pH, and culture |

**FIGURE 7-10.** Further laboratory investigation of diseases identified by clinical examination or the initial evaluation shown in Figure 7-9. Bone biopsy can be useful in patients with atypical forms of osteoporosis, osteomalacia, or renal osteodystrophy. ALT—alanine transaminase; AST—aspartate transaminase; 25-OHD—25-hydroxyvitamin D; PTH—parathyroid hormone.




## B. SECONDARY CONTRIBUTORS TO OSTEOPOROSIS IDENTIFIED IN 173 OTHERWISE HEALTHY WOMEN WITH OSTEOPOROSIS*

| Disorder of Bone or Mineral Metabolism | Number |
|---|---|
| Hypercalciuria | 17 |
| Malabsorption | 14 |
| Hyperparathyroidism (primary and secondary) | 12 |
| Vitamin D deficiency (<30 nmol/L) | 7 |
| Exogenous hyperthyroidism | 4 |
| Cushing's disease | 1 |
| Familial benign hypercalcemia | 1 |
| Total number of new diagnoses | 56 |

**One patient had two unrelated diagnoses.*

**FIGURE 7-11.** Secondary contributors to osteoporosis identified in 173 otherwise healthy women with osteoporosis. The data are represented in schematic (**A**) and tabular (**B**) form. In patients who present to the clinic with low bone mineral density, a laboratory evaluation is useful in uncovering diagnoses that may be responsible for the osteoporosis, or that may affect the design of treatment. In this study, 173 women who had osteoporosis without obvious cause had laboratory measures including a complete blood count, chemistry profile, 24-hour urine calcium, 25-hydroxyvitamin D, and parathyroid hormone [6]. A substantial fraction was found to have secondary contributors to osteoporosis. (*Adapted from* Tannenbaum *et al.* [6].)

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8

# *Bone Densitometry in Osteoporosis Care*

*Michael R. McClung*

Bone density testing has achieved a prominent role in the evaluation of patients with or at risk for osteoporosis. The original bone methods for measuring bone density were developed several decades ago. The transition of these technologies from the research setting to the patient care arena began as the relationships between bone density and fracture risk were defined and when a definition of postmenopausal osteoporosis, based on bone density values, was provided. The availability of treatments to increase bone density and reduce fracture risk propelled bone density testing into the clinical limelight. Clinical guidelines advocate widespread use of bone density testing, and indications for osteoporosis treatment are now based on bone density values. The number of bone density machines in clinical use has markedly increased in the past 5 years. Testing is no longer confined to the specialist's office or radiology centers. Machines are in primary care clinics and in small communities, and testing is available in pharmacies and grocery stores and at health fairs. New technologies and devices have been developed, with each providing different types of information. An international society now exists to address the needs of the clinical bone density community.

This chapter focuses on the most important applications of common bone density testing devices used in daily clinical practice, including the assessment of fracture risk, the diagnosis of osteoporosis, and the monitoring of bone density values over time. The principles of the technologies are reviewed, and current recommendations for interpretation are presented. In addition, some of the pitfalls and challenges encountered in applying these techniques are discussed, including lessons learned from three case examples.

# Technology

**BONE DENSITY TECHNOLOGIES**

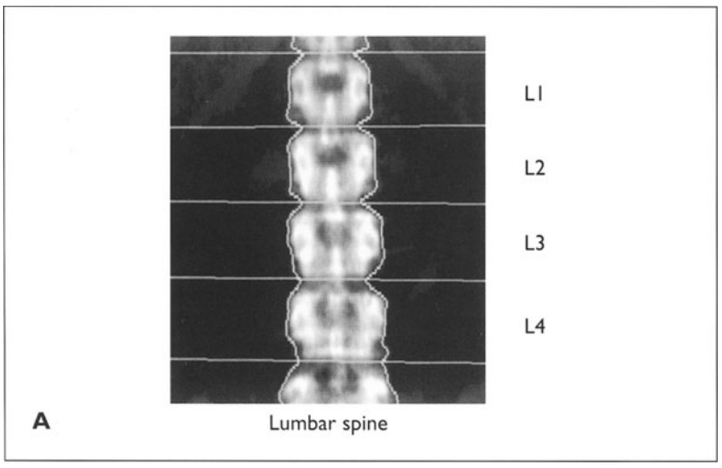
| Technology | Sites Measured |
|---|---|
| X-ray photon absorptiometry | |
| Dual-energy (DEXA) | Spine, proximal femur, forearm, total body, fingers |
| Single-energy (SEXA) | Forearm, heel |
| Quantitative computed tomography (QCT) | |
| Central | Spine, proximal femur |
| Peripheral | Forearm |
| Quantitative ultrasound (QUS) | |
| Transmission | Heel |
| Reflective | Forearm, lower leg, fingers |

**FIGURE 8-1.** Bone density technologies. Several different technologies have been adapted to measure bone density. Absorptiometry techniques are based on the principle that passage of photons through the skeleton is inhibited (photons absorbed) by the mineral component of bone. Current absorptiometry devices use x-rays as the photon source. Dual-energy x-ray absorptiometry (DEXA) uses photons of two different energies to factor out the absorption by soft tissue. With this technique, the bone mineral content (BMC) can be measured in important central skeletal sites, such as the spine and hip, in peripheral sites, such as the heel, forearm, and fingers, or in the total skeleton. Single-energy x-ray absorptiometry (SEXA) devices require immersing the measured site (forearm or heel) in a water bath to factor out the soft tissue contribution to photon absorption. These devices have generally been supplanted by DEXA.

Both DEXA and SEXA measure the BMC of a discrete region in the skeleton, and these results are expressed as grams of mineral [1]. The area of the two-dimensional image of that region is computed in units of $cm^2$. An estimate of bone mineral density (BMD) is then derived by dividing the BMC of the measured region by the area of that region, an "areal" density measurement is derived that is expressed in units of $g/cm^2$. Since the depth of bone is not accounted for in the test, this is not a true measure of bone density, and absorptiometry techniques are affected by bone size. Individuals with larger bones (men compared with women, blacks compared with whites) will have higher areal bone density measurements, as will small people. DEXA measurements of the spine and hip are the most useful techniques in clinical practice because of the extensive experience with their use in both observational and treatment studies.

Computed tomography (CT) is designed to measure true tissue density. When appropriately calibrated, standard CT scanners can measure bone density in the central portion of a lumbar vertebral body that is composed solely of trabecular bone, and the results are expressed in $g/cm^3$. Although a powerful technique, quantitative CT is less useful in the clinic than is DEXA because the relationship of the values acquired and fracture risk is less well defined, and because very few osteoporosis treatment studies enrolled patients on the basis of CT measurements. Specialized software is now available for measuring bone density in the proximal femur by CT scanning. Other CT machines measure bone density in peripheral skeletal sites, such as the forearm. This technique can distinguish between cortical and trabecular compartments of bone. This device is being used primarily in research settings, and its role in clinical practice is just being evaluated.

Two types of quantitative ultrasound (QUS) are used to assess skeletal status [2]. Transmission ultrasound techniques determine the speed of sound waves or changes in the properties of these waves as they pass through a bone. The calcaneus is the site most commonly measured with this technique. It was hoped that ultrasound measurements would provide information about the structure or quality of bone in addition to the amount of bone present. Current transmission ultrasound techniques, however, are influenced predominantly by bone mass and have not been shown to provide unique information about bone quality. Reflective ultrasound techniques measure the speed of sound transmission along the surface of long bones, such as the tibia, radius, or phalanges. The results of these tests probably are influenced primarily by the amount and nature of the cortical shell of these long bones.



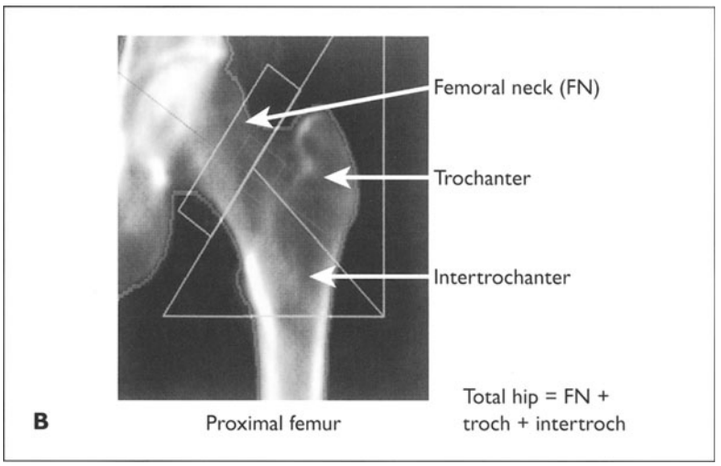




**FIGURE 8-2.** Dual-energy x-ray absorptiometry (DEXA) measurements of the lumbar spine and proximal femur. Shown are DEXA images of the lumbar spine and proximal femur, generated by converting the photon count rate measured at each pixel (point) into a gray scale image. **A,** Spine measurements are made in the lumbar region. Testing in the thoracic spine is not possible because of the overlying sternum. The accuracy of DEXA measurements is related to the size of the region measured. The accuracy of measurements in individual vertebral bodies is less than that in a larger region; thus, the composite of the L1-4 or L2-4 is recommended for clinical use. **B,** In the proximal femur, measurements are made in the femoral neck and the trochanter regions. The total hip measurement is a combination of the femoral neck, trochanter, and intertrochanteric regions. DEXA machines also report a value for Ward's region, but this measurement is not useful in clinical practice because of this site's very small size. The computer software locates the bone edges, and the technologist verifies or adjusts the location of the specific region of measurement. Proper and meaningful measurements require consistent positioning and alignment of the patient on the scanning table and appropriate placement of the regions of interest markers.

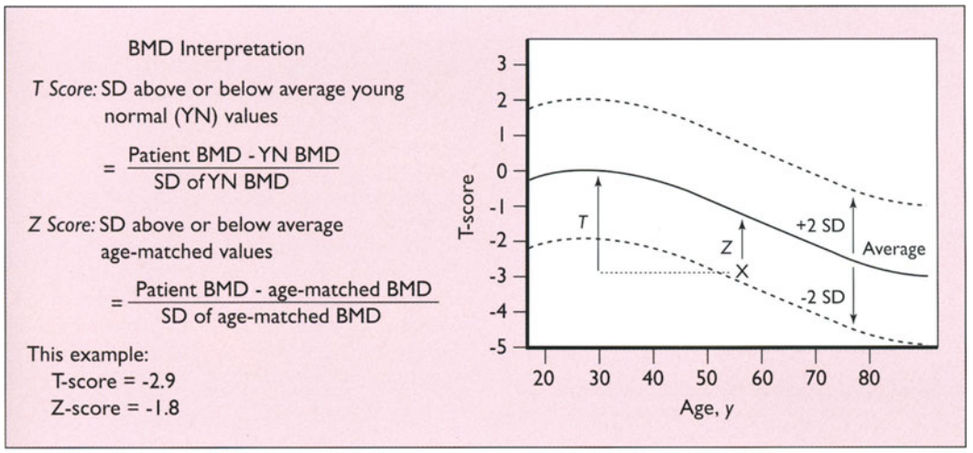



**FIGURE 8-3.** Reporting of bone mineral density (BMD) results. Bone density values are usually expressed in relation to reference populations in standard deviation (SD) units. This figure depicts the average bone density values in women of different ages (*solid curved line*) and the values 2 SD above or below that average value (*broken curved lines*). The T-score is the number of SD above (a positive number) or below (a negative number) the average value in young adults. The T-score values decline with age. When compared with average age-matched values, a patient's results are described as Z-scores. In this example, a 58-year-old woman (results shown at X) has a T-score of -2.9 (2.9 SD below the average value of young women) and a Z-score of -1.8.

T-scores are currently used to diagnose osteoporosis. These values are very dependent on the reference database used for calculation. Differences in the average young normal values, and especially the SD between databases, can result in large differences in T-score values in patients with the same BMD values. The average BMD value is lower in Asian women than in white ones, and the SDs of the values in the population are similar. For any BMD value in $g/cm^2$, a lower T-score is calculated with the use of the white database than an Asian database. The risk of spine fracture is similar for Asians and whites with the same absolute BMD value, and the prevalence of osteoporosis is underestimated if an Asian database is used. Z-score values lower than -2 are abnormal for a patient and increase the possibility of an underlying medical cause of bone loss. However, many patients with diseases or metabolic abnormalities that cause bone loss have normal Z-scores, and a normal value does not exclude the presence of a contributing cause of bone loss.

**POTENTIAL USEFULNESS OF BMD TESTING**

- Predicting fracture risk
- Making the diagnosis of postmenopausal osteoporosis
- Confirming radiologic osteopenia
- Following skeletal status over time
- Evaluating skeletal effects of medical problems
- Identifying patients for treatment
- Encouraging patients to begin therapy
- Monitoring response to therapy
- Enhancing adherence to therapy

**FIGURE 8-4.** Uses of bone mineral density (BMD) measurements. Bone mineral density measurements can be used for several clinical purposes, many of which are listed in this figure [3]. The most important use is the prediction of fracture risk, in conjunction with other risk factors for fracture. A T-score value of -2.5 or lower is now used to diagnose postmenopausal osteoporosis. Based on results from prospective clinical trials, clinical guidelines have proposed thresholds for treatment based on bone density values. The thresholds for intervention differ, depending on the presence of other risk factors for bone loss or fracture, and are not necessarily the same as the threshold used for diagnosis. Bone density testing has been shown to influence a patient's decision to accept a recommendation to begin therapy. Following changes in BMD values over time or in response to treatment requires special attributes of testing.

## Predicting Fracture Risk

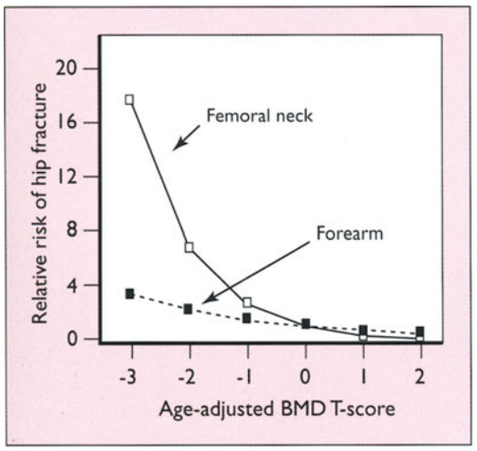



**FIGURE 8-5.** Use of bone mineral density (BMD) to predict fracture risk. Depicted is the relationship between BMD measured at either the forearm or the femoral neck and the subsequent risk of hip fracture. The data were obtained in a large observational study in white American women older than 64 years of age [4]. At very low BMD values, small changes are associated with large differences in fracture risk. There is no specific "fracture threshold" at which risk becomes apparent. There is a progressive gradient of risk with lower BMD. For each standard deviation (SD) decrease in age-matched BMD in the hip, the relative risk of hip fracture increased 2.6 fold. At an age-matched T-score of -3 in the femoral neck, the risk of hip fracture is 17.6 times higher in such women than in women of equivalent age with an average BMD value for their age. A 1 SD decrease in forearm density increases the risk of hip fracture by a factor of 1.5, and fracture risk is increased 3.4 fold in women whose forearm BMD is 3 SD below average for age. Bone density measurement at a specific site more strongly predicts fracture risk at that site than do measurements at other parts of the skeleton.

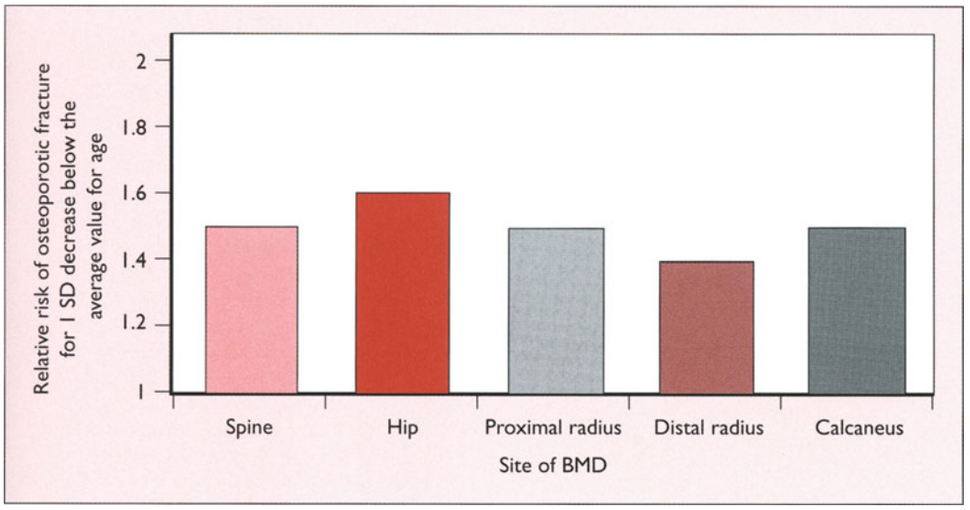



**FIGURE 8-6.** Prediction of fracture risk with bone mineral density (BMD). Shown is the relationship between fracture risk and BMD measured at various skeletal sites with different technologies. These data, based on the meta-analysis by Marshall *et al.* [5], demonstrate that a value 1 SD below the average value for age is associated with 1.5-fold increased risk of experiencing any osteoporotic fracture, irrespective of where bone density is measured. This relationship is stronger than is the association of cholesterol and heart disease and is at least as strong as the association of high blood pressure and risk of stroke. The prediction of fracture risk is stronger in older (higher risk) patients than in younger adults, and the prediction of short-term (5 to 10 years) risk is better than that of very long-term risk (more than 15 years or lifetime risk) [3].

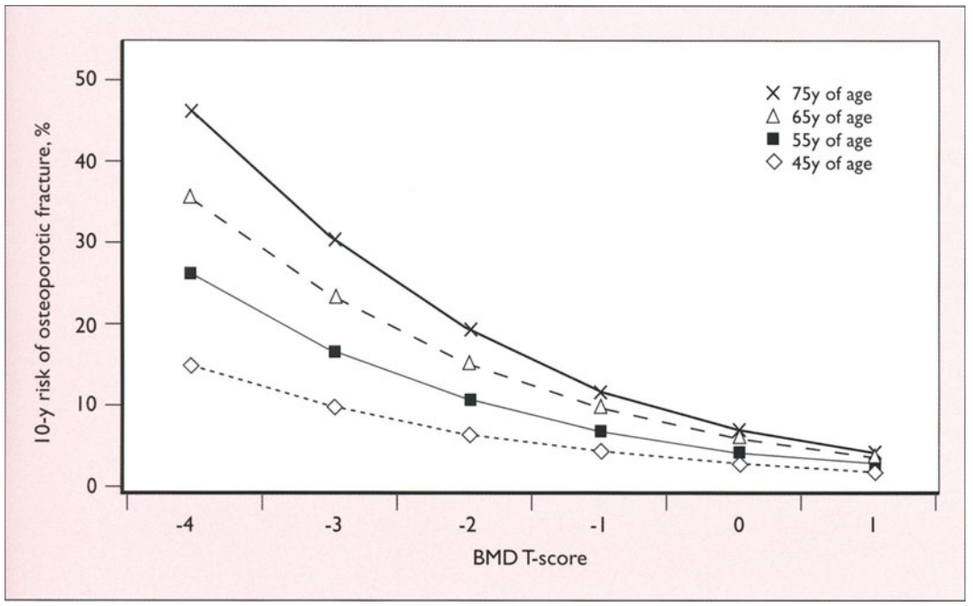
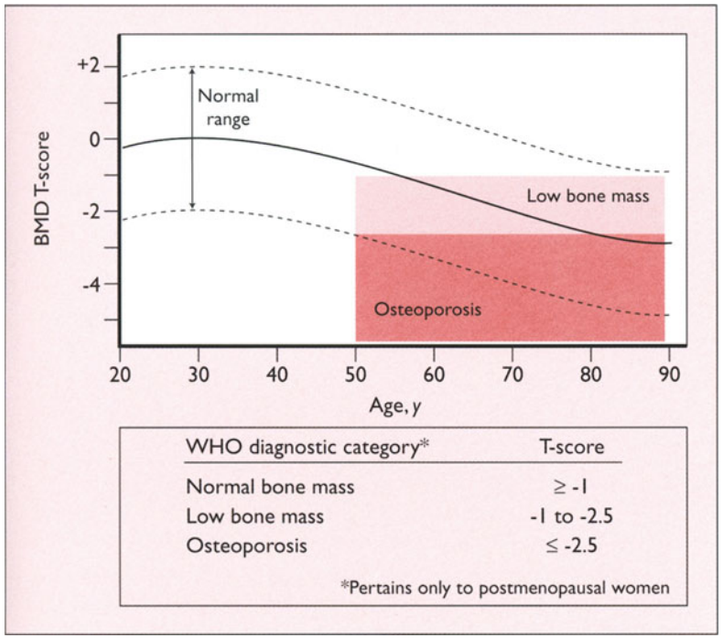



**FIGURE 8-7.** Interaction between bone mineral density (BMD), age, and other risk factors for predicting fracture risk. The relationship between T-scores and fracture risk is significantly influenced by the age of the patient [6]. At all ages, postmenopausal women with low T-scores are more likely to have a fracture than are women with higher T-scores. For a given T-score, though, older women are at greater risk for fracture than are younger women. Part of this effect of age on fracture risk is due to the greater likelihood of falls in very elderly adults. However, a major part of this difference may be related to the fact that older women have experienced more bone loss than have younger women with the same T-score. As a result, older women have more deterioration of skeletal structure and bone quality and thus a more fragile skeleton than that of younger women, but these changes in the quality of bone are not detected by bone density tests.

Other BMD-independent risk factors modify the relationship between bone density and fracture risk. The most important of these is a history of previous fracture. Having a previous spine fracture increases the probability of having another spine fracture by four to five fold and the probability of having another hip fracture by two fold [7]. Small body size, a parental history of hip fracture, and the presence of medical causes of bone loss also affect fracture risk. Low BMD is thus an important determinant of fracture risk, but not the only one. Bone density values must be considered and interpreted in the context of these other clinical variables in the assessment of fracture risk and determination of whom to treat. Current clinical guidelines have different T-score thresholds for treatment, depending on the presence or absence of other risk factors [8–10].

# Diagnosing Osteoporosis




| WHO diagnostic category* | T-score |
|---|---|
| Normal bone mass | ≥ -1 |
| Low bone mass | -1 to -2.5 |
| Osteoporosis | ≤ -2.5 |

*Pertains only to postmenopausal women

**FIGURE 8-8.** Diagnostic categorization of bone mineral density (BMD) values. The World Health Organization (WHO) proposed that the diagnosis of osteoporosis in postmenopausal women be defined as a T-score of -2.5 or lower and that values between -1 and -2.5 be defined as low bone mass or osteopenia [11]. Values higher than -1 were defined as normal. These diagnostic categories were initially proposed for epidemiologic purposes (comparing BMD values among different populations), not for clinical diagnosis or decision-making. Subsequent clinical trials have confirmed the usefulness of the diagnostic threshold for osteoporosis, and the value of -2.5 or lower in the PA spine or proximal femur is now widely accepted as the definition of osteoporosis. Note that this diagnostic category applies only to healthy postmenopausal women because the relationship between BMD and fracture risk is not well known in other forms of osteoporosis (*eg*, glucocorticoid-induced osteoporosis) or in younger women.

The use of the term *osteopenia* based on BMD values is now widespread in bone density reports. Without incorporating other risk factors (especially age), this term has little practical clinical value. Note that the category of osteopenia overlaps the true normal range for young women (the average ± 2 SD or T-scores between -2 and +2). Values between -1 and -2 are below average but not below normal, do not necessarily suggest that bone loss has occurred, and, in young postmenopausal women, are associated with low current fracture risk [6].

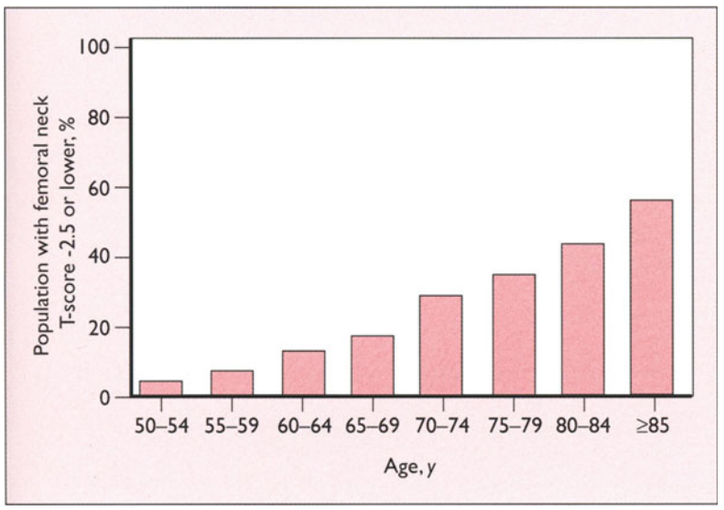



**FIGURE 8-9.** Prevalence of osteoporosis in women based on bone mineral density values. Bone density in the proximal femur was measured in a very large population-based survey in the United States (NHANES III) [12]. The proportion of this population with femoral neck T-score values at or below -2.5 increased exponentially with advancing age from 4% at age 55 years to about 50% at age 85. This NHANES database is recommended for calculating T-score values in the proximal femur.

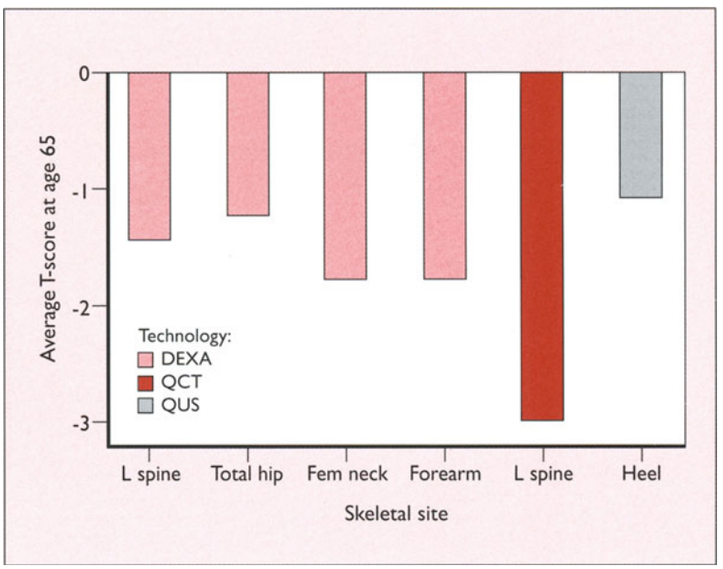



**FIGURE 8-10.** Disparity in T-score values among different bone mineral density (BMD) tests. T-scores measured at different skeletal sites or with different techniques yield different values because of differences in normative databases, variable rates at which bone is lost from different skeletal sites, and marked differences in the standard deviation of BMD values in young adult populations. T-scores from all skeletal sites cannot be used interchangeably because T-score values from different sites or obtained with different techniques do not provide the same information about fracture risk. The average T-scores calculated with different techniques in healthy 65-year-old women vary greatly, as shown in this figure [13]. The World Health Organization diagnostic categories are meant for use only with measurements by dual-energy x-ray absorptiometry (DEXA) in the proximal femur and probably the postero-anterior (PA) spine. The International Society for Clinical Densitometry (ISCD) recommends that only T-scores in the PA spine, femoral neck, and total hip be used for diagnostic categorization [14]. Values from other sites may be useful for prediction of risk. QCT—quantitative computed tomography; QUS—quantitative ultrasound.

**A. REASONS FOR LOW BONE DENSITY**

- Advanced age
- Accelerated bone loss
- Low-normal peak bone mass
- Failure to acquire optimal peak bone mass because of
  - Small size
  - Heredity
  - Late or missed puberty

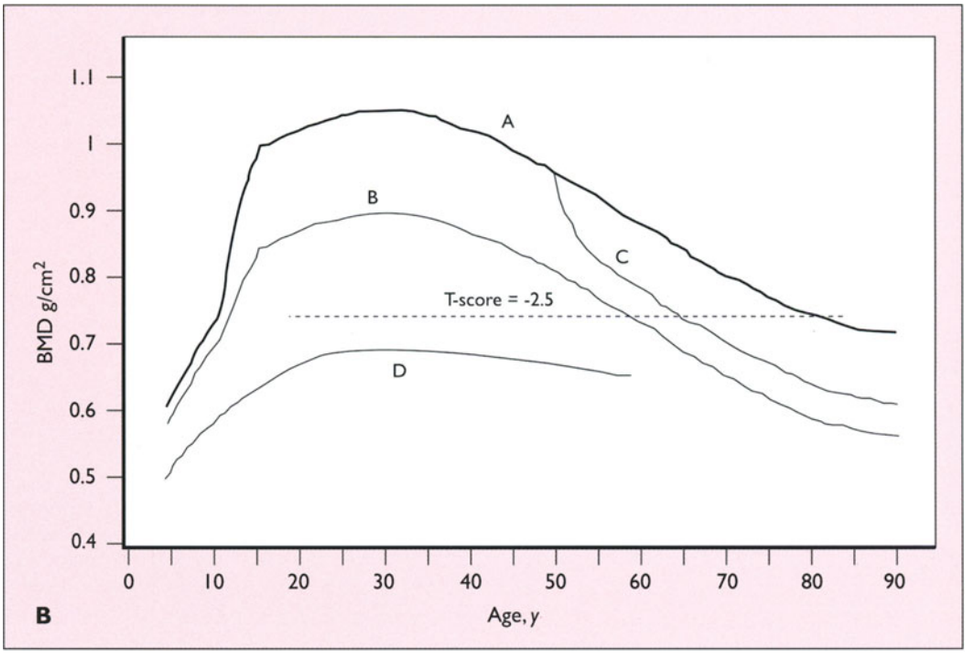



**FIGURE 8-11. A,** Mechanisms of developing low bone mineral density (BMD). An individual may develop low BMD in several ways. Since bone loss occurs in all women after menopause, and with aging in both men and women, simply becoming older increases the probability of having osteoporosis. **B,** The age at which women with average BMD values have values consistent with osteoporosis is about 85 years (*A*). Women with low-normal values at menopause will have values in the osteoporosis range in their late 50s or early 60s (*B*). Patients who lose bone mass more quickly because of medical or metabolic problems will develop osteoporosis more quickly (*C*). A small number of people will never develop normal amounts of bone because of genetic reasons or because of impaired bone growth during childhood or adolescence (*D*). These patients will have values consistent with osteoporosis without ever losing bone mass. Therefore, low BMD does not always mean that bone loss has occurred.

**INTERPRETATION OF BONE DENSITY RESULTS**

Premenopausal women
- Normal values are ±2 SD of average young normal values (T-score -2 to +2)

Children and adolescents
- Compare with age-matched reference values

*Note: T-scores are not relevant before skeletal maturation is reached.*

**FIGURE 8-12.** Interpreting bone mineral density (BMD) values in other groups of patients. The World Health Organization criteria for the diagnosis of osteoporosis apply only to healthy postmenopausal women. For healthy premenopausal women or young men, the normal range includes T-score values between -2 and +2. Values below -2 are best described as "low bone density." These patients should be evaluated for the presence of either medical or genetic causes of low BMD. It is not appropriate to use T-scores to describe BMD values in individuals who have not attained skeletal maturity. The expected BMD values in a healthy 10-year-old boy would be equivalent to a T-score of -4, but the boy would not have osteoporosis. In children or adolescents, we compare BMD values with age- and gender-specific reference ranges, ideally adjusted for body size and, in adolescents, for pubertal status. Values below -2 are unexpectedly low. SD—standard deviation.

**BONE DENSITY DIAGNOSIS OF OSTEOPOROSIS IN MEN**

- No firm guidelines exist for diagnosing osteoporosis in men
- In some studies, fracture risks in men and women are the same at the same absolute bone density values, suggesting that the same (female) database should be used to calculate T-scores in both genders
- Using a male database of calculated T-scores provides a more realistic estimate of the prevalence of osteoporosis and fractures in men

**FIGURE 8-13.** Diagnosing osteoporosis in men. Controversy exists about the appropriate bone mineral density (BMD) threshold for diagnosing osteoporosis in men because men have larger bones, their bone mass is greater, and peak areal BMD values by dual-energy x-ray absorptiometry (DEXA) are higher in men than in women. Thus, for any given absolute BMD value (in g/cm$^2$), a T-score derived from a male database will be lower than the T-score calculated from a female database. Some studies demonstrate that fracture risks in men and women are the same at the same absolute bone density values, suggesting that the same (female) database should be used to calculate T-scores in both genders [15]. However, using a male database of calculated T-scores provides a more realistic estimate of the prevalence of osteoporosis and fractures in men in the general population. European experts and societies suggest using a T-score threshold of -2.5, based on a female database, to diagnose osteoporosis in older men, while the International Society for Clinical Densitometry (ISCD) recommends using T-scores calculated with a male database [3,16].

**DIFFERENTIAL DIAGNOSIS OF LOW BONE DENSITY**

Osteoporosis
- Primary
- Secondary

Osteomalacia

Osteogenesis imperfecta

Marrow-based diseases (eg, myeloma, mastocytosis)

**FIGURE 8-14.** Differential diagnosis of low bone mineral density (BMD). Most BMD testing devices measure the bone mineral content of a defined area of the skeleton. Metabolic bone diseases other than osteoporosis that are characterized by a decreased amount of bone (osteogenesis imperfecta, myeloma) or by very poorly mineralized bone, such as osteomalacia, are also associated with low BMD values. The pathophysiology and especially the treatment of these disorders is very different from that of osteoporosis. Thus, a low BMD value is not necessarily diagnostic of osteoporosis. The correct interpretation of a dual-energy x-ray absorptiometry (DEXA) T-score of -2.5 or lower is that the result is "consistent with the diagnosis of osteoporosis." These other diseases must be excluded before the patient can be said to have osteoporosis or before osteoporosis treatment is begun.

# Monitoring Change

**MONITORING INTERVAL CHANGE**

Requires skeletal site that changes (spine, hip)

Very careful quality control is a necessity
- Same machine, scan speed, etc.
- Exact re-positioning

Interpretation of serial values requires knowing reproducibility of bone density laboratory (CV or coefficient of variation)

Minimal significant change: best expressed in $g/cm^2$ (not %)
- 95% confidence 2.77 × CV

**FIGURE 8-15.** Monitoring interval change. Following serial changes in bone mineral density (BMD) values is a challenge for bone density laboratories and for clinicians [17]. The changes that occur over a time interval of 1 to 2 years are quite small (1% to 3% without treatment and 2% to 6% with treatment). The two important requirements for following changes are to measure a site that actually changes in response to the clinical circumstance or treatment and to use a test that is very precise or reproducible. Although BMD tests in the forearm and heel are quite precise, they are not useful for monitoring treatment because the values change very little in response to current osteoporosis therapies. The International Society for Clinical Densitometry (ISCD) recommends the lumbar spine as the preferred site for monitoring treatment response, with the total hip region being an alternative when the spine cannot be measured [18]. Other skeletal sites are not recommended for monitoring.

Exquisite quality control in the BMD laboratory is necessary if serial testing is to be clinically useful. Differences in calibration among different types of dual-energy x-ray absorptiometry (DEXA) machines, and even different machines from the same manufacturer, make it difficult to compare results acquired on different DEXA machines unless the specific machines have been cross-calibrated. Reproducibility should be evaluated in each bone density laboratory by performing duplicate tests on multiple patients and calculating the coefficient of variation (CV) of repeat measurements. The least significant change (LSC)—the smallest change between two values that is statistically significant—can be calculated from the CV. To be 95% confident that two measurements are not the same, the difference has to be greater than 2.77 times the CV. This value is the LSC. It is best to express LSC in absolute terms ($g/cm^2$), rather than as percent change. In experienced laboratories, the LSC is about 0.04 $g/cm^2$ in the lumbar spine and 0.05 $g/cm^2$ in the proximal femur.

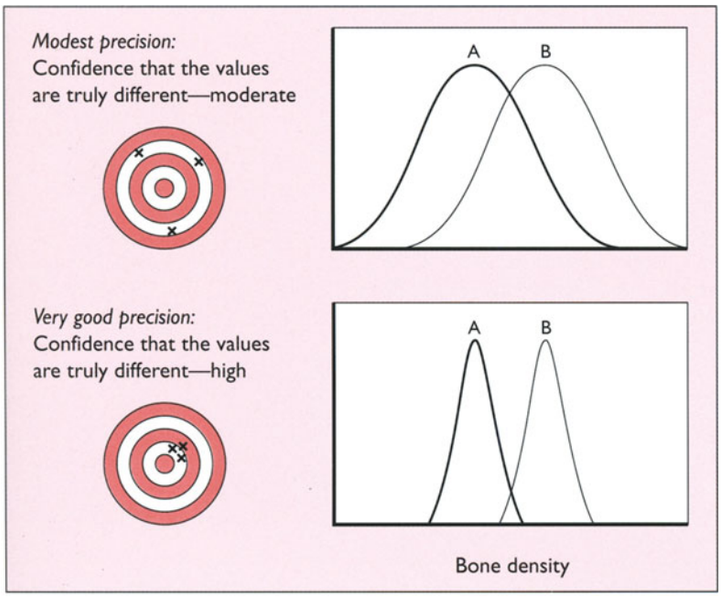
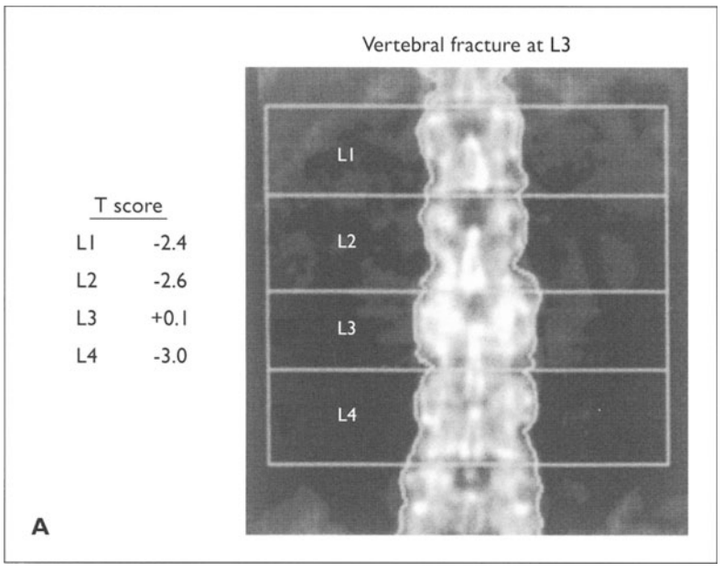


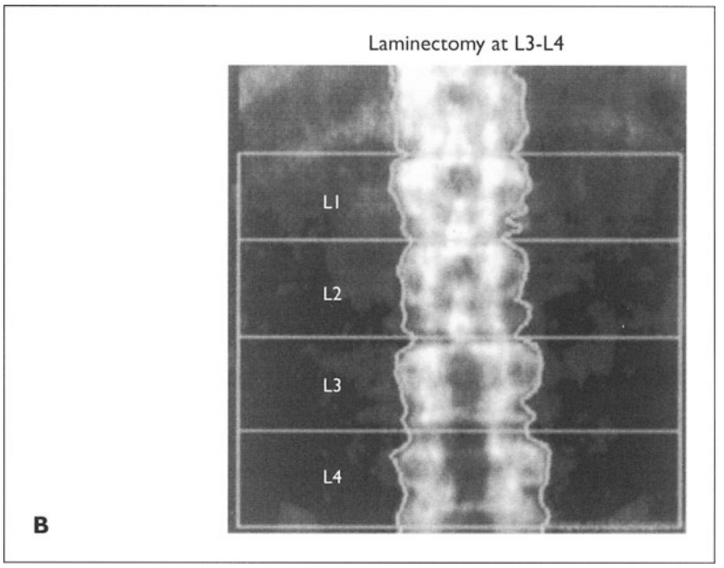

**FIGURE 8-16.** Precision affects the ability to monitor interval change. Precision is a measure of how close repeated measurements are in the same patient if no change has occurred. In the *top example*, each of the darts is in the target, but they are in different parts of the target. Precision is only modestly good, and the confidence interval (the noise of measurement) is quite broad (depicted by the *curved lines* that overlap substantially) for the two bone mineral density (BMD) values (*A and B*) from the same patient. The statistical (and clinical) confidence that the two values are truly different is limited by the poor precision. When precision is excellent (*lower example*, where the darts are closely placed even though they are not all in the bull's eye), the confidence that the same two measurements are truly different is much greater. Unless the reproducibility of BMD testing in a laboratory is known, it is not possible to interpret the significance or relevance of differences in serial test results.

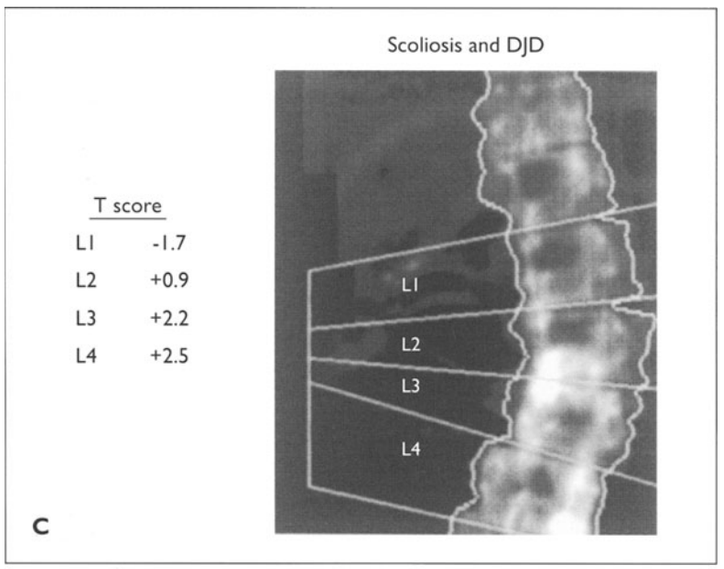
**FACTORS INFLUENCING PRECISION**

- Machine related
  - Drift in calibration
  - Mechanical defects
- Patient related
  - Internal or external artifacts
  - Skeletal deformities
  - Marked change in weight
  - Patient movement during scanning
- Operator related
  - Inconsistent positioning or analysis

**FIGURE 8-17.** Factors influencing precision. Reproducibility of repeat testing can be affected by changes in the performance characteristics of the bone density machine that can occur with movement or repair of the instrument or a defect in the x-ray generator or detector. Changes in the patients, such as internal or external artifacts or an interval fracture in the lumbar spine or hip, can cause apparent bone mineral density differences that do not reflect a true change. Appropriate and consistent positioning of the patient by the technologist is the most important determinant of excellent reproducibility. A quality control protocol is necessary, and a careful review of the bone density scans and images at the time of interpretation is required to optimize performance of a bone density laboratory and the usefulness of the test results.



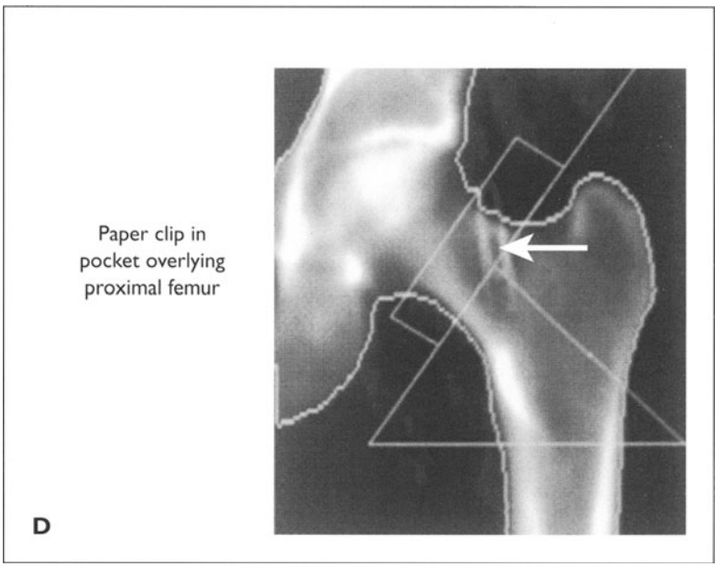




**FIGURE 8-18.** Four examples of dual-energy x-ray absorptiometry (DEXA) artifacts are shown. **A,** A vertebral fracture of L3 increases the bone mineral density (BMD) value in that vertebral body. The presence of this artifact necessitates that the T-score be calculated from L1 + L2 + L4. **B,** The BMD value of L1-4 would be spuriously low because the spinous process at L3-4 has been removed by a laminectomy. The result in the L1-2 region would be a more appropriate value to report. **C,** Moderate scoliosis and degenerative changes result in an overestimate of BMD in the spine. In such patients, values in the proximal femur must be used to assess fracture risk or for diagnostic categorization. **D,** External artifacts overlying the region of measurement interfere with the accuracy of the test. Marked changes in weight (more than 50 pounds) between tests may also induce error into the measurement and complicate the interpretation of observed changes. All these potential confounding variables must be taken into account when one compares sequential BMD test results.

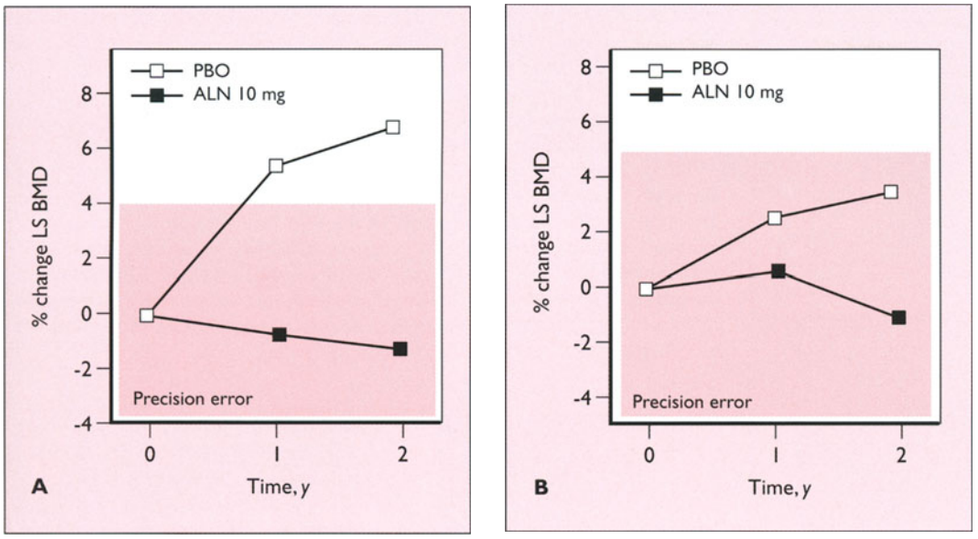



**FIGURE 8-19.** Bone mineral density (BMD) response to treatment and least significant change (LSC). Shown are the average BMD responses over 2 years in the lumbar spine (**A**) and femoral neck (**B**), measured by dual-energy x-ray absorptiometry (DEXA) in postmenopausal women treated with alendronate 10 mg daily or placebo (PBO) [19]. The top and bottom of the *shaded area* depicts the LSC at each skeletal site. The values in the spine and hip in the patients who received calcium plus placebo decrease by 1% to 2% over 2 years. These changes are statistically significant in the large groups of patients studied. However, the changes do not exceed the LSC, and the slow rate of loss would not be observed in individual patients. The average increase in BMD in the spine is greater than the LSC. A significant increase would be observed in most, but not all, individual patients. In contrast, the average change in the femoral neck does not exceed the LSC, and most patients would not be observed to have a significant increase in BMD at that site even after 2 years of treatment. However, fracture reduction is observed, even in the patents in whom an increase in BMD cannot be confirmed [19]. Thus, not seeing an increase in BMD in response to treatment is not evidence of treatment failure. Our current BMD tests are simply not sensitive enough to see changes in all patients who are responding. Observing a true decrease in BMD (greater than the LSC) warrants a review of whether and how the patient is taking the medication and whether medical or metabolic problems exist.

**PERIPHERAL BMD TESTING**

Substantial discordance exists between T-score values among different skeletal sites and the various BMD technologies because of
- Different normative databases
- Differences in SD compared with average BMD in young adults
- Differences in peak bone mass among skeletal sites
- Site-specific differences in rates of age-related bone loss

Peripheral BMD cannot be used to
- Diagnose osteoporosis
- Decide whom to treat
- Monitor response to therapy

Peripheral tests can be used to predict fracture risk

**FIGURE 8-20.** Peripheral bone mineral density (BMD) testing. These testing devices are attractive because of their portability, lower costs, and, for ultrasound units, the lack of radiation exposure. Their role in clinical practice is still being evaluated [20]. Currently, they cannot be used to diagnose osteoporosis, determine whom to treat, or monitor response to therapy. Some of these devices have been validated for predicting fracture risk. As we develop risk-based thresholds and criteria for treatment, these devices may acquire a more important role in daily clinical practice. For similar reasons, central BMD technologies, such as quantitative computed tomography of the spine or lateral spine measurements by dual-energy x-ray absorptiometry (DEXA), cannot be used for diagnosis. SD—standard deviation.

# Indications

**MEDICARE REIMBURSEMENT FOR BONE DENSITY TESTS***

Reimbursement is allowed in these situations
- An estrogen-deficient woman at clinical risk for osteoporosis
- An individual with vertebral abnormalities indicated by radiograph to be indicative of osteoporosis, low bone mass, or vertebral fracture
- A person receiving long-term glucocorticoid therapy equivalent to prednisone 7.5 mg/d for more than 3 mo
- An individual with primary hyperparathyroidism
- A person being monitored to assess the response to or efficacy of an FDA-approved osteoporosis drug therapy
- Follow-up testing at 2 y

**Bone Mass Measurement Act of 1998.*

**FIGURE 8-21.** Medicare reimbursement for bone density testing. In 1998, Congress passed the Bone Mass Measurement Act, which mandated reimbursement for bone density testing by Medicare carriers for specified indications, listed in the figure [21]. Estrogen-deficient women of Medicare age are eligible for testing. Repeat testing is allowed at intervals of 2 years to monitor treatment response. More frequent testing may be allowed for patients at high risk for bone loss, such as those beginning to receive glucocorticoid therapy. FDA—U.S. Food and Drug Administration.

**INDICATIONS FOR BONE DENSITY TESTING**

- Postmenopausal women with fragility fractures
- All women older than 65 y of age
- Younger postmenopausal women with risk factors for fracture or low bone density, especially
  - Thinness
  - Family history of hip or spine fracture

**FIGURE 8-22.** Indications for bone mineral density (BMD) testing in women. Several national societies and organizations have made recommendations about when BMD is appropriate [8–10]. Recently, the United States Preventative Services Task Force made recommendations based on a careful review of the evidence of clinical usefulness of BMD testing [22]. All of the guidelines suggest that routine testing for women aged 65 years and older is appropriate. Although the specific recommendations differ somewhat among the guidelines, all recommend measuring BMD in younger postmenopausal women with other important risk factors for bone loss or fracture. Testing of postmenopausal women and older men who have experienced fragility fractures is generally recommended because having such a fracture is a risk factor for having osteoporosis and another fracture. None of the guidelines suggest routine measurement for all perimenopausal or premenopausal women. No agreement has yet been reached on the indications for testing in men.

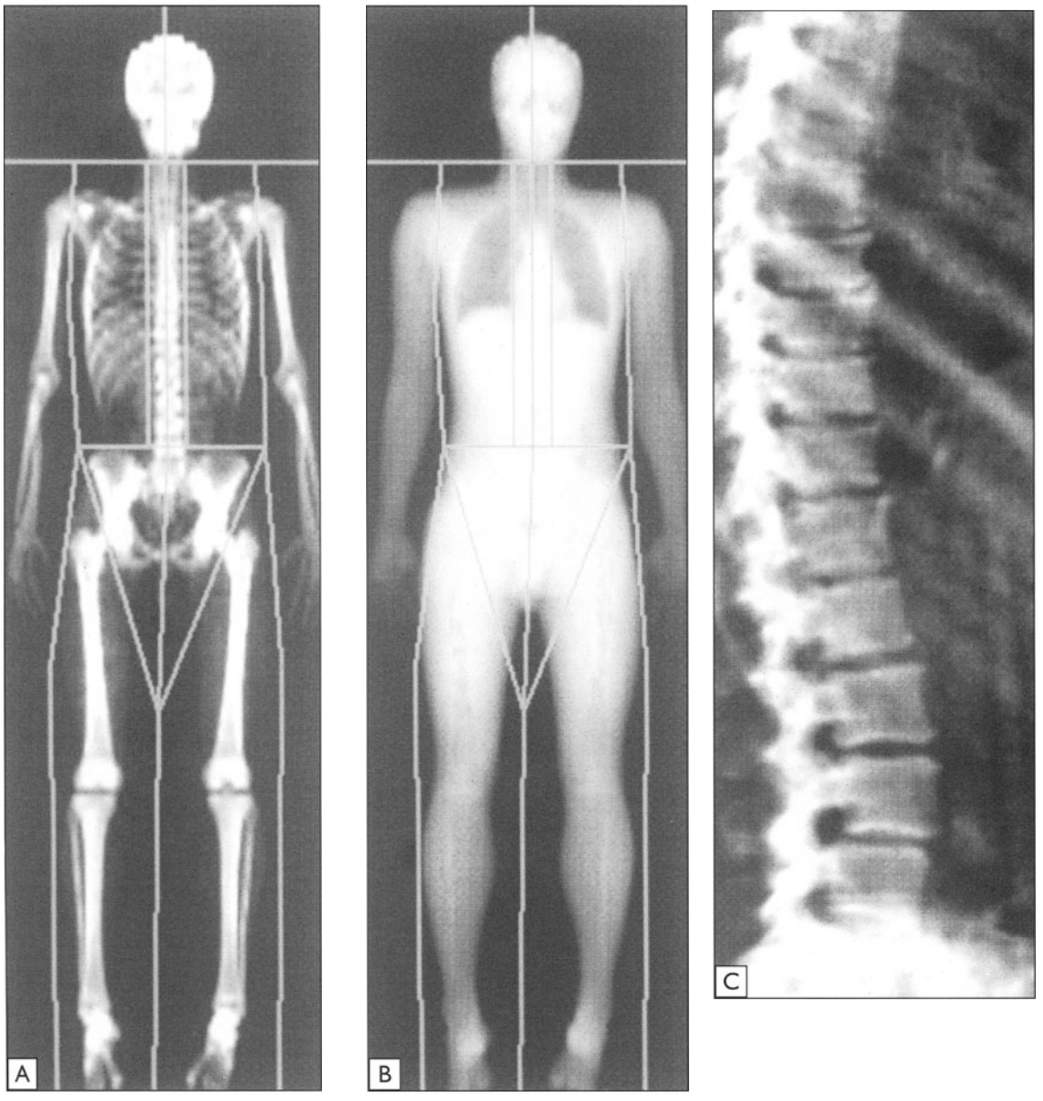
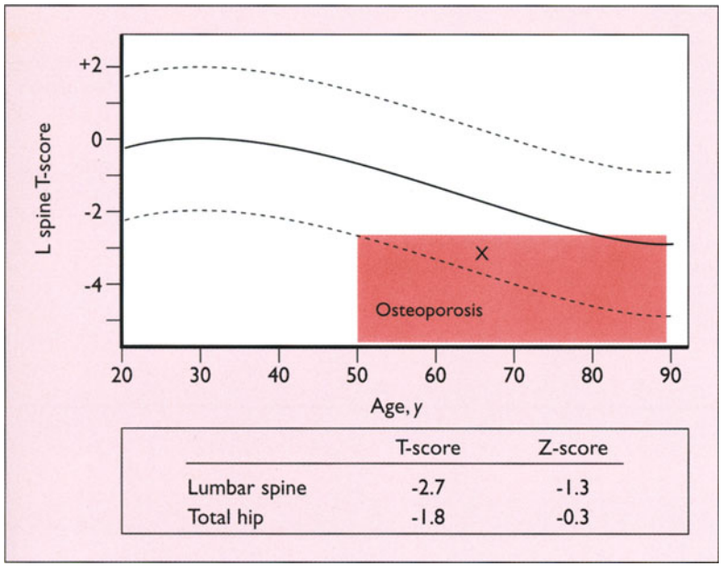



**FIGURE 8-23.** Other uses of dual-energy x-ray absorptiometry (DEXA). DEXA testing can also be used to measure total body calcium or bone density (**A**). This has limited utility in the management of adults at risk for osteoporosis but is often helpful in assessing the skeletal status of children. **B,** The same technique can accurately measure body composition, distinguishing body fat, lean tissue, and bone. **C,** Special software allows imaging of the spine from T4 to L4 to evaluate the contours and shape of the vertebral bodies, allowing the presence of vertebral fractures to be determined [23].

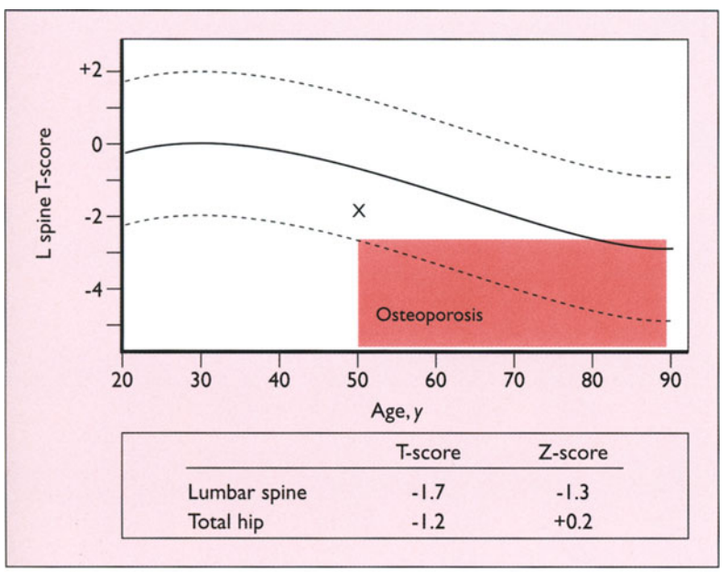
# Case Examples




| | T-score | Z-score |
|---|---|---|
| Lumbar spine | -2.7 | -1.3 |
| Total hip | -1.8 | -0.3 |

**FIGURE 8-24.** *Case Study 1.* This 67-year-old woman took estrogen for the first 5 years following menopause. She has not experienced a fracture and has no evidence of medical causes of bone loss. Her intake of calcium and vitamin D is adequate. She weighs 148 pounds, is 66 inches tall, and has not lost height. Her mother experienced vertebral fractures at age 65.

This patient's spine bone mineral density (BMD) values are consistent with the diagnosis of osteoporosis, while the value in the total hip is in the lower portion of the normal range for young women. The value in the spine makes her a candidate for osteoporosis therapy. Although these values are not unexpected for her age, it would be important for the practitioner to exclude other causes of low BMD before beginning osteoporosis treatment.




| | T-score | Z-score |
|---|---|---|
| Lumbar spine | -1.7 | -1.3 |
| Total hip | -1.2 | +0.2 |

**FIGURE 8-25.** *Case Study 2.* This 50-year-old woman has not taken estrogen since menopause at age 48. She weighs 115 pounds and is 5 feet 2 inches tall. She has not had fractures, but her mother experienced vertebral fractures at age 65. She is healthy, does not smoke, exercises regularly, and takes appropriate amounts of calcium and vitamin D. She was told that she has "moderate osteopenia," has lost 30% of her bone density, has the bones of a 75-year-old woman, and is at high risk for fracture.

This patient has bone mineral density (BMD) values in the low-normal range for young women. It would be important to determine whether she has medical or metabolic reasons for bone loss. However, her family history of osteoporosis and small body size are risk factors for low BMD. Without knowing peak bone mass, a definitive statement about how much bone loss has occurred cannot be made on the basis of the results of a single BMD test. The average rate of bone loss in the lumbar spine is 1.5% to 2 % per year for the first few years following menopause. It is probable that peak BMD value in her spine was in the low-normal range and that she had experienced only modest bone loss since menopause. Although her BMD values are the same as the average value in the 70-year-old woman, her risk of fracture is much lower than that of the older woman, who would have experienced loss of bone mass and bone structure to arrive at that T-score. While therapy might be considered to protect this patient from further bone loss, it is unlikely that she has a significant underlying skeletal disorder, and her risk for fracture over the next 5 years is very low.

## CASE EXAMPLE 3

Bone density T-scores:
- L spine -3.5
- Total hip -2.8

Laboratory values:
- Serum calcium, 9.0 mg/dL
- Albumin, 4.0 g/dL
- High normal alkaline phosphatase
- 24-hour urinary calcium, 22 mg
- Serum total testosterone, 680 ng/mL

**FIGURE 8-26.** *Case Study 3.* This 55-year-old man experienced a metatarsal fracture while running. Radiographs suggested low BMD. He is healthy, with normal sexual function, no change in weight, and no gastrointestinal symptoms. His calcium intake is 1200 mg daily.

This patient has unusually low bone mineral density (BMD) values for a man his age. An evaluation for secondary causes of bone loss is appropriate. His serum chemistry and serum testosterone values are normal, but his urinary calcium excretion is surprisingly low. Further evaluation included a measurement of serum 25-hydroxyvitamin D, which was less than 9 ng/mL (normal >20). Intact parathyroid level was 115 pg/mL (reference range 10–65). Anti-endomysial antibodies were positive, and a duodenal biopsy demonstrated findings consistent with celiac disease. He was treated with a gluten-free diet, calcium, and high doses of vitamin D. One year later, his BMD T-score values were -2.0 in the spine and -1.8 in the total hip region. Although the BMD values were quite low, this patient did not have osteoporosis, and treatment with drugs for osteoporosis was not appropriate. It is important to exclude other causes of low BMD before concluding that a patient with a low T-score has osteoporosis.

**SUMMARY**

Bone density testing is now an important tool for assessing skeletal status and fracture risk in patient at risk for osteoporosis

T-score values must be combined with other risk factors to assess fracture risk

Only DEXA of hip or spine can be used to diagnose osteoporosis

Exquisite quality control is required for adequate interpretation, especially when serial studies are being evaluated

**FIGURE 8-27.** Summary. Bone mineral density (BMD) testing is now an important and valuable tool for evaluating patents at risk for osteoporosis. Bone mineral content can be accurately assessed, but other important components of bone quality, including the structure and mechanical properties of bone are not captured in the bone density test result. When combined with other risk factors, bone density values are strongly correlated with fracture risk in untreated older adults. While a variety of bone density technologies may predict fracture risk, only dual-energy x-ray absorptiometry (DEXA) values of the hip and spine are recommended for diagnosing osteoporosis in postmenopausal women. T-score values cannot be compared among different types of bone density machines. Following changes in bone density over time is both a technical and a clinical challenge, and exquisite quality control is required for adequate interpretation of serial studies. Understanding both the technical aspects of bone density tests and the clinical relevance of the results optimizes the application of these technologies to the care of patients.

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# 9

# *Estrogen-dependent Bone Loss and Osteoporosis*

*Robert Lindsay and Felicia Cosman*

The relationship between estrogen deficiency and osteoporosis was first formally described in the 1940s. Since then, the biologic relationship between estrogen deficiency and bone loss has been explored in detail. With the onset of estrogen deficiency, increased activation of bone remodeling is seen at the bone histomorphometric level, with a consequent increase in biochemical markers of bone remodeling in blood and urine. Bone loss occurs most rapidly in the first 5 years after overt menopause, especially at cancellous bone sites, but estrogen-dependent bone loss continues throughout life. Mechanisms include increased monocyte and osteoblast production of a variety of cytokines, including tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, and the receptor activator of nuclear factor κB ligand (RANKL), among others, all of which promote osteoclastogenesis and osteoclast activity, the first event in the remodeling process. In addition to an increased remodeling rate, permanent loss of bone tissue requires an imbalance between bone formation and resorption, with a net loss of bone occurring during each remodeling cycle.

Consistently, it has been shown in many randomized controlled trials that estrogen administration to postmenopausal women reduces biochemical markers and histomorphometric evidence of bone remodeling as well as improves bone mass at all skeletal sites. For many years, the evidence of the ultimate impact of estrogen and hormone administration on fractures was observational, with only a few small prospective clinical trials in agreement. Several years ago, the results of the Heart and Estrogen/progestin Replacement Study (HERS) shed some doubt on estrogen's effect on fracture occurrence. However, the results of the Women's Health Initiative (WHI) now confirm that hormone replacement therapy reduces the risk of all osteoporosis-related fractures in postmenopausal women of average age 62 years whose osteoporosis status is unknown. Other systemic risks of hormone therapy have been confirmed, however, and constitute important limitations to more widespread use of hormone therapy.

This chapter highlights the most important data concerning the biology of estrogen deficiency, the effects of estrogen intervention on intermediate markers (bone mass and bone turnover) and fractures, and the importance of estrogen for the skeletal status of men.

# Biology of Estrogen Deficiency

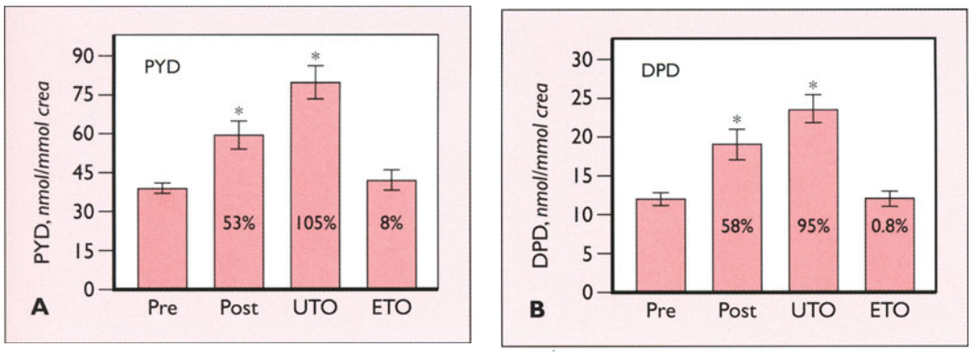



**FIGURE 9-1.** Evaluation of the effects of menopause as well as osteoporosis and estrogen replacement through measurement of levels of pyridinoline (PYD) and deoxypyridinoline (DPD) in four groups of women [1]. Mean urinary concentrations of the hydroxypyridinium cross-links PYD (**A**) and DPD (**B**) in postmenopausal (Post) healthy women and untreated (UTO) and estrogen-treated (ETO) women with postmenopausal osteoporosis compared with premenopausal (Pre) healthy women. Column inserts denote percentage change of mean value compared with normal premenopausal controls (Pre). *Bars* represent standard error of the mean (SEM). Asterisks indicate $P$ values < 0.01. Levels of both PYD and DPD were 53% to 58% higher in postmenopausal women than in premenopausal women. Both PYD and DPD were significantly higher in the UTO group than in Post ($P < 0.01$).

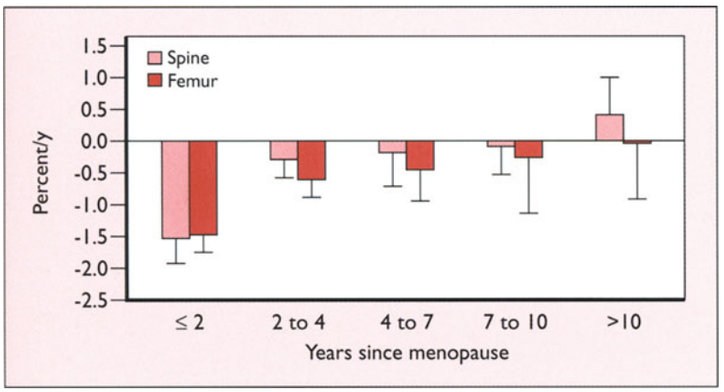



**FIGURE 9-2.** The importance of early bone loss and its association with estrogen deficiency shown in these data associating years since menopause and rates of bone loss [2]. Longitudinal data for spontaneous loss of lumbar and femoral neck bone mineral density (BMD) in women receiving placebo ($n = 71$; mean age 56.3±4.4 y) are combined from two randomized, controlled trials. The highest rates of bone loss occurred in women close to the menopause. A significant relationship between years since menopause and BMD loss was observed at the spine ($r = 0.34$; $P < 0.01$) and femoral neck ($r = 0.25$; $P < 0.001$). (*Adapted from* Bjarnason *et al.* [2].)

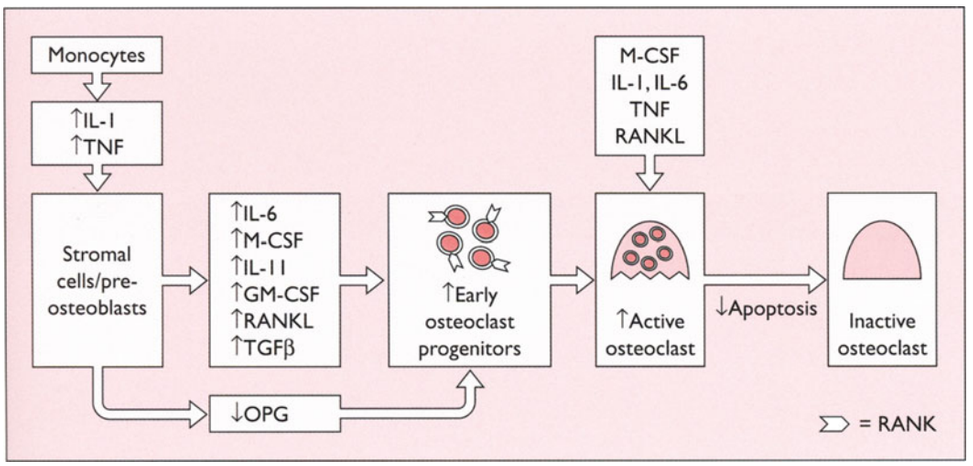



**FIGURE 9-3.** Several cellular changes occur in estrogen deficiency that cause a net loss of bone tissue: increased osteoblastogenesis, increased osteoclastogenesis, increased lifespan of osteoclasts, reduced lifespan of osteoblasts, and reduced lifespan of osteocytes. Illustrated here is the influence of various cytokines on osteoclast formation and lifespan, one of the key mechanisms by which estrogen causes increased bone resorption and remodeling [3–12]. In the absence of estrogen, the production of tumor necrosis factor (TNF) by monocytes increases, and cells of the stromal/osteoblastic lineage become more sensitive to interleukin-1 (IL-1). IL-1 and TNF stimulate stromal cells and preosteoblasts to release IL-6, macrophage colony-stimulating factor (M-CSF), IL-11, granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor beta (TGFβ), and the receptor activator of nuclear factor κB ligand (RANKL), all factors that stimulate the proliferation of osteoclast precursors or osteoclastogenesis. The receptor activator of nuclear factor κB (RANK) is expressed in osteoclast progenitors and promotes osteoclastogenesis when it binds to RANKL.

In addition, estrogen deficiency may negatively influence osteoprotegerin (OPG). OPG is a soluble decoy receptor for RANKL, and lower levels of OPG result in more RANKL available to bond to RANK and stimulate osteoclast formation and activity. M-CSF, IL-1, TNF, IL-6, and RANKL also inhibit osteoclast apoptosis, thereby increasing the lifespan of osteoclasts. By similar mechanisms, estrogen deficiency also leads to increased osteoblastogenesis, reduced lifespan of osteoblasts, and reduced lifespan of osteocytes, all of which contribute to postmenopausal osteoporosis. (These effects are not depicted in this schematic.)

# Effects of Estrogen on Intermediate Markers (Bone Mass and Turnover)

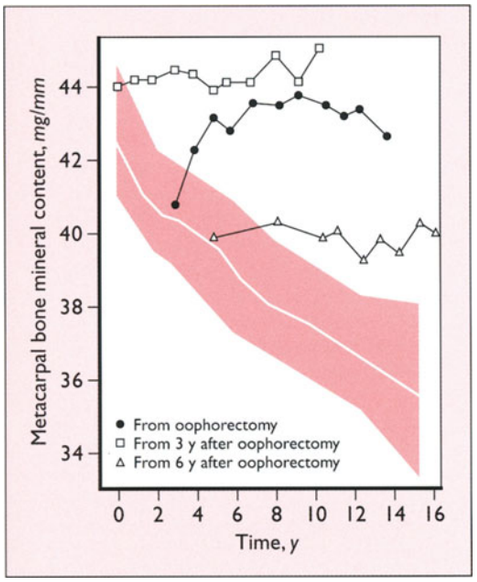



**FIGURE 9-4.** Estrogen prevents or slows bone loss and may modestly increase bone mineral density (BMD), whenever it is initiated, as demonstrated in this landmark study by Lindsay *et al.* [13]. This prospective, double-blind trial investigated the effects of long-term treatment with estrogen replacement therapy (24.8 μg mestranol, an estrogen formulation that is no longer widely used in postmenopausal women) or placebo in 120 women who began therapy 2 months, 3 years, or 6 years after oophorectomy for benign pelvic disease in their late 40s. In a further analysis of the data from the original trial, long-term (>10 y) estrogen replacement therapy significantly reduced the rate of loss of metacarpal bone mineral content. The earlier the treatment was begun, the more beneficial was its effect on bone loss, since bone that was already lost could not be replaced to any significant extent. These results indicate that estrogen replacement therapy should be initiated as soon as possible after the onset of menopause in order to maximize its beneficial long-term effects. (*Adapted from* Lindsay *et al.* [13].)

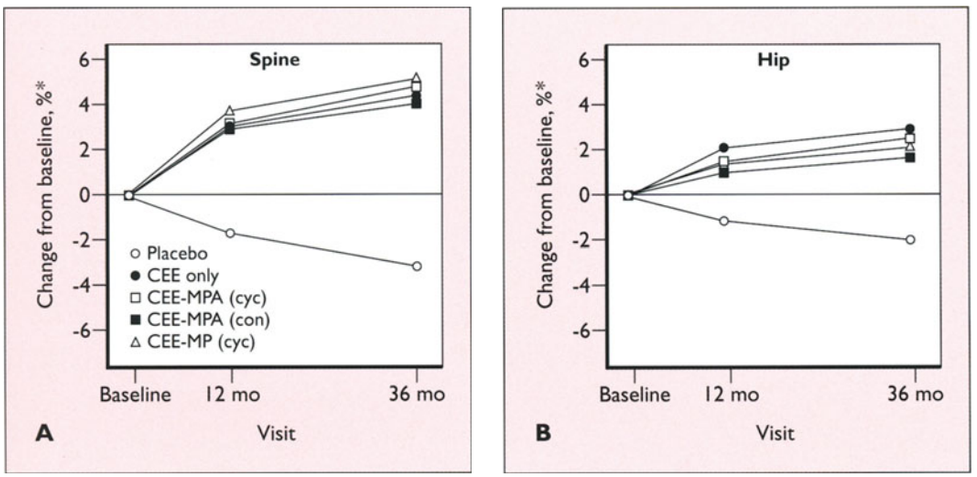
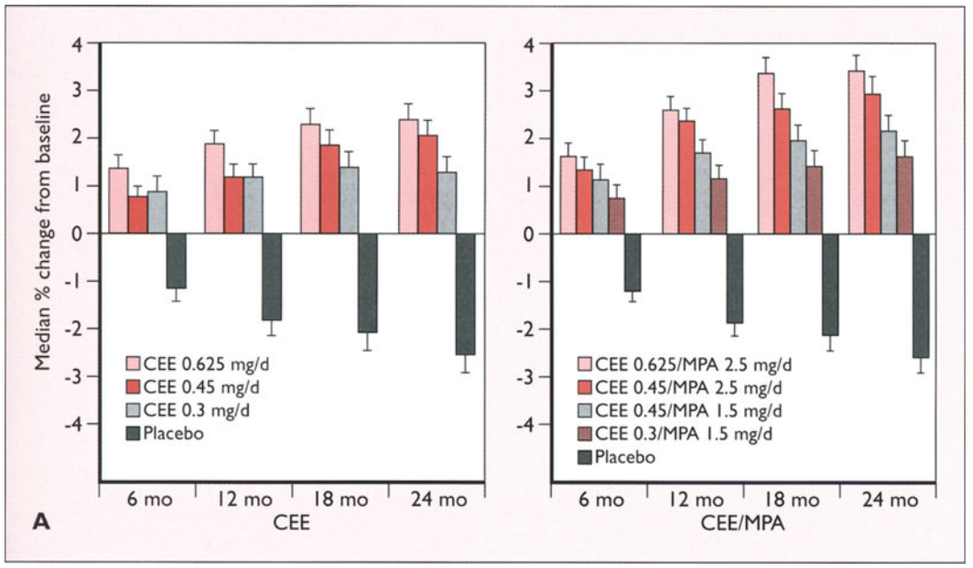
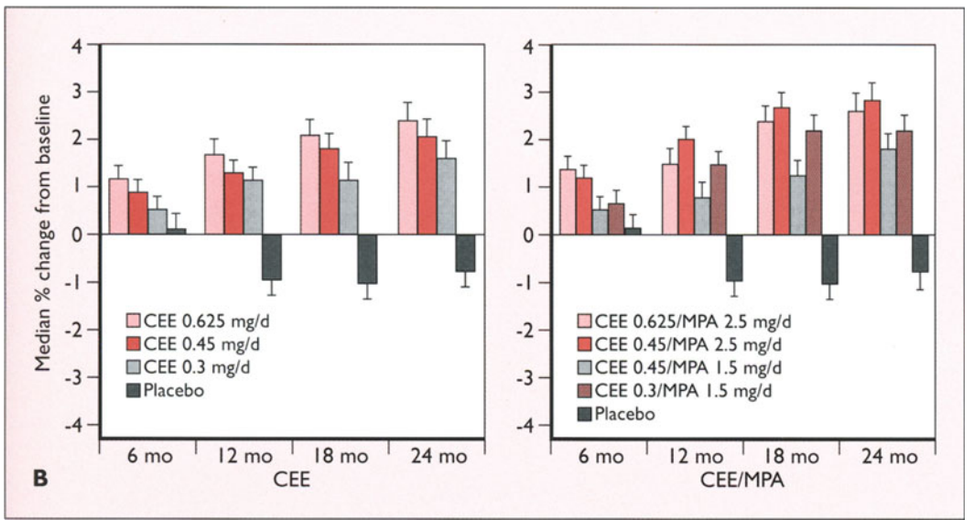
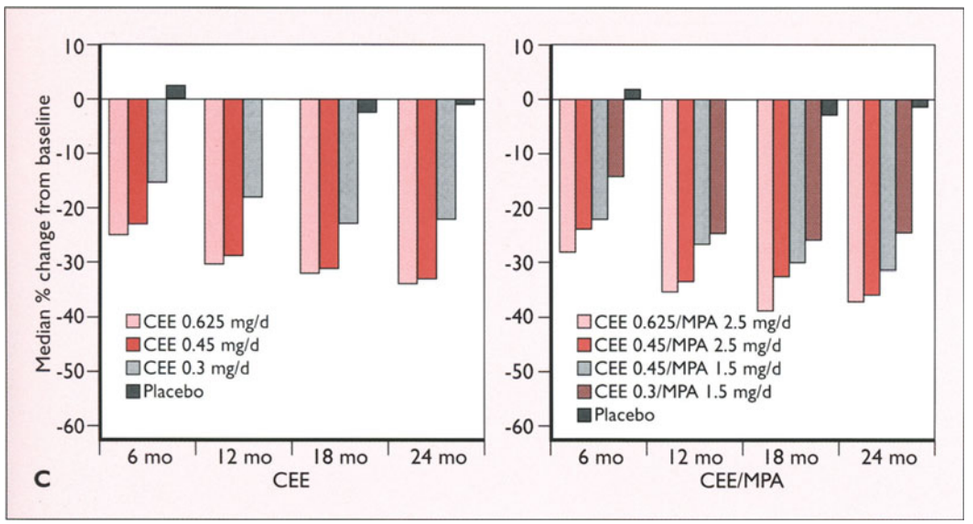



**FIGURE 9-5.** In the Postmenopausal Estrogen/progestin Intervention (PEPI) Trial, a 3-year, double-blind, placebo-controlled, multicenter trial, 875 women aged 45 to 64 years were randomly assigned to one of four treatment groups: 1) conjugated equine estrogen (CEE) 0.625 mg/d; 2) CEE 0.625 mg/d plus medroxyprogesterone acetate (MPA) 10 mg/d for 12 d/mo; 3) CEE 0.625 mg/d plus MPA 2.5 mg/d; 4) CEE 0.625 mg/d plus 200 mg micronized progesterone (MP) 12 d/mo; or 5) placebo. **A** and **B**, By 36 months, women who were compliant with the placebo regimen had lost an average of 2.8% of spinal bone mineral density (BMD) and 2.2% of hip BMD, whereas those found to be compliant with any active regimen had gained approximately 4% in the spine and 2% in the hip. There was a significant increase in hip and spine BMD in each active treatment group from baseline to the 12-month visit, and for each active treatment group from the 12-month to the 36-month visit. Among the patients compliant with therapy, results of all active regimens were significantly different from placebo, but no active treatment was significantly different from other active treatments. (***B*** *Adapted from* Writing Group for the PEPI Trial [14].)




**FIGURES 9-6.** There is evidence that doses of hormone replacement therapy lower than those most commonly prescribed may be effective in preventing bone loss in older women; however, the effects of lower doses of hormone replacement therapy in early postmenopausal women have not been well studied. The Women's Health, Osteoporosis, Progestin, Estrogen (Women's HOPE) Trial was a prospective, randomized, double-blind, placebo-controlled, multicenter trial that investigated the efficacy and safety of lower doses of conjugated equine estrogen (CEE) alone and with continuous medroxyprogesterone acetate (MPA) in early postmenopausal women (who were within 4 years of their last menstrual period) [15]. The 2-year bone substudy used a subpopulation of the Women's HOPE Trial ($n$ = 822) to evaluate the skeletal effects of lower doses of CEE and CEE/MPA. The substudy included the following groups: CEE 0.625 mg; CEE 0.45 mg; CEE 0.3 mg; CEE 0.625 mg/MPA 2.5 mg; CEE 0.45 mg/MPA 2.5 mg; CEE 0.45 mg/MPA 1.5 mg; CEE 0.3 mg/MPA 1.5 mg; and placebo. These graphs include data from the intent-to-treat population, which consisted of all women randomized to treatment who recorded taking at least 1 dose of the study drug and had at least 1 bone mineral density (BMD) measurement after baseline.

After 2 years, women assigned to all of the active treatment groups had significant gains from baseline ($P < 0.001$) in spine BMD (**A**). These changes were statistically different from those in the placebo group. In addition, adding 2.5 mg MPA to 0.625 mg or 0.45 mg CEE significantly increased spine BMD relative to CEE alone ($P < 0.05$). These data demonstrate that lower doses of CEE and CEE/MPA effectively prevent bone loss in the spine in early postmenopausal women. All estrogen and estrogen/progestin dose combinations also increased BMD in the hip (**B**) and total body. Moreover, estrogen and hormone therapy in all doses reduced biochemical markers of bone turnover, including serum osteocalcin (**C**) and urinary cross-linked N-telopeptide (**D**).

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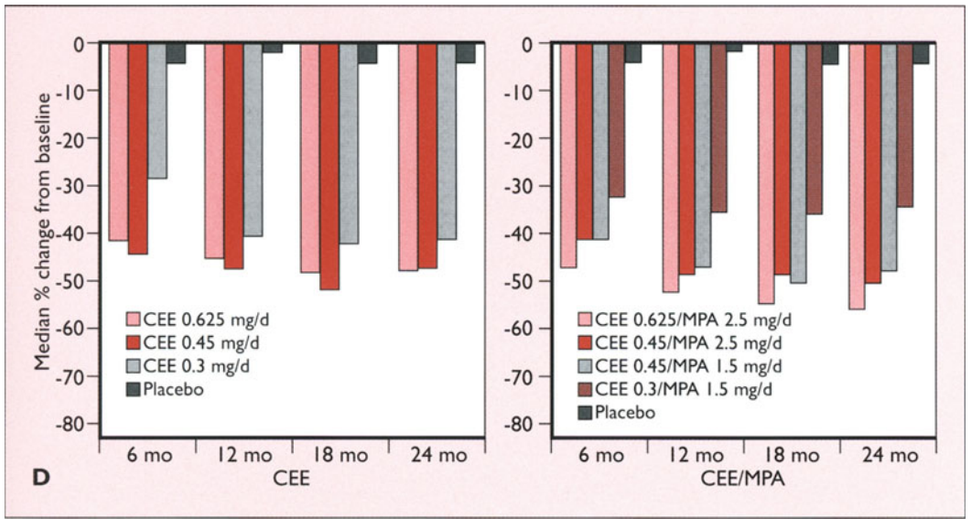


**FIGURES 9-6.** *(Continued)*

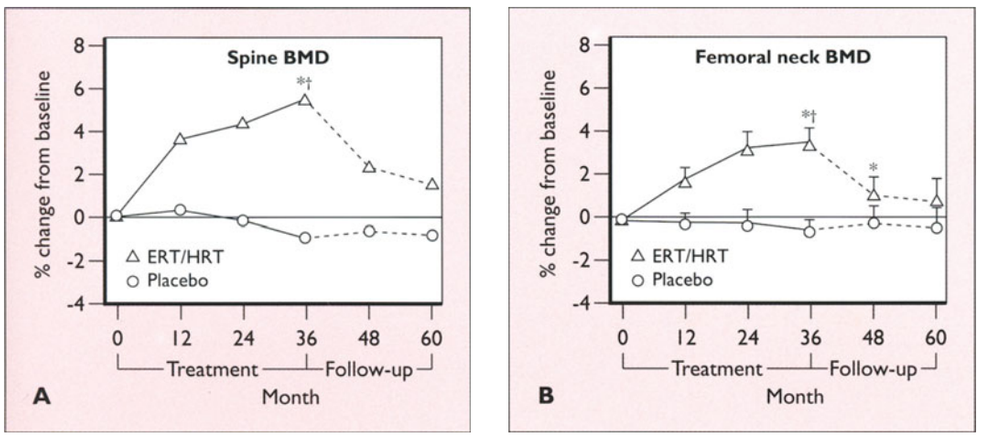


**FIGURE 9-7. A** and **B**, A 3-year randomized prospective study (STOP IT) was conducted in 489 postmenopausal women, 65 to 77 years of age, to test the efficacy of 3 years of treatment with estrogen replacement therapy (ERT)/hormone replacement therapy (HRT)—conjugated equine estrogen 0.625 mg/d alone or with medroxyprogesterone acetate 2.5 mg/d in women with an intact uterus. At the end of 3 years of treatment, therapy was discontinued and the women were asked to volunteer for 2 years of follow-up. Analyses were performed in the 178 women who completed the fifth year of the study. Discontinuing ERT/HRT in these older postmenopausal women resulted in rapid bone loss—almost 6% in the spine and about 2% in the femoral neck. BMD—bone mineral density. (Adapted from Gallagher *et al.* [16].)

## Effects of Estrogen Intervention on Fracture Occurrence

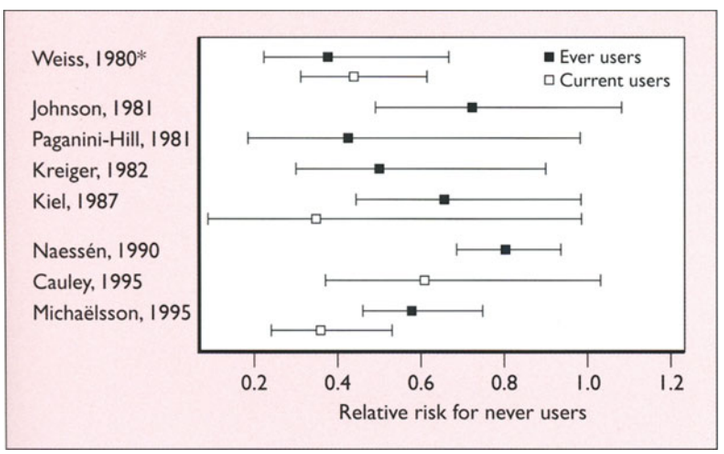


**FIGURE 9-8.** A number of case-control and cohort studies have provided epidemiologic evidence that estrogen replacement therapy (ERT)/hormone replacement therapy (HRT) reduces the risk of hip fracture. These studies suggested that hip fractures may be reduced by 20% to 60% in ERT/HRT users compared with nonusers [17–21].

**ESTROGEN AND VERTEBRAL FRACTURES**

Long-term study of ERT in oophorectomized women
One hundred women treated with either estrogen or placebo
Followed for 9.5 y
Radiographs at conclusion of the study
Significantly fewer vertebral deformities
Less height loss in estrogen-treated women

**FIGURE 9-9.** The first randomized, controlled clinical trial data suggesting that estrogen reduced fracture risk came from the study by Lindsay [21a], who showed in a small population of ovariectomized women that estrogen could reduce the appearance of new vertebral fractures. ERT—estrogen replacement therapy.

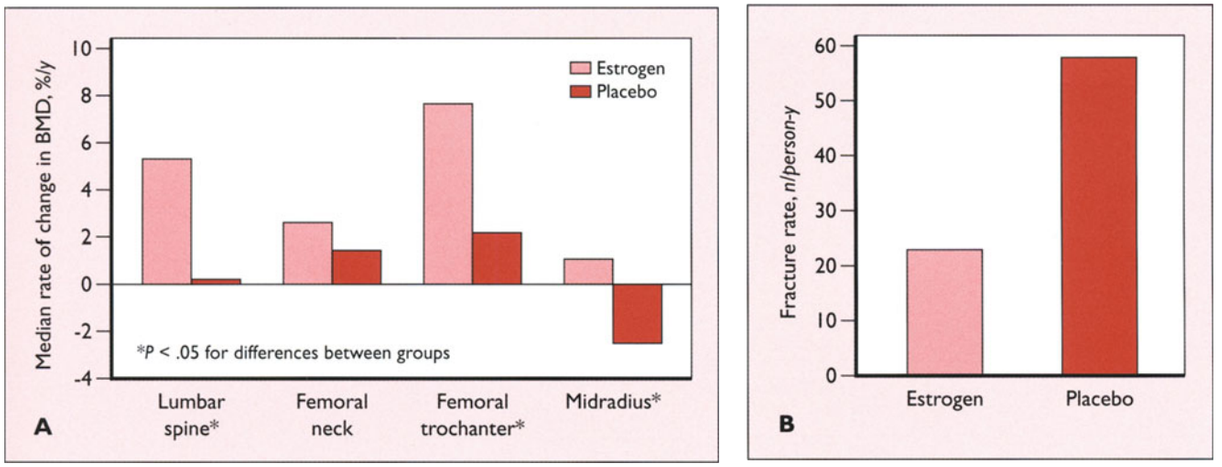


**FIGURE 9-10. A** and **B**, Estrogen's effects are not dependent on the route of administration. Lufkin *et al.* [22] demonstrated in a small 1-year study that transdermal estrogen could also increase bone mass and reduce the risk of vertebral fracture. BMD—bone mineral density. (*Adapted from* Lufkin *et al.* [22].)

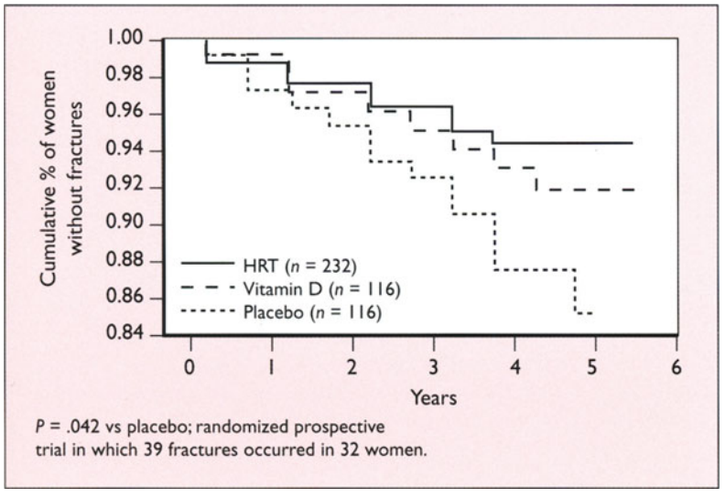


**FIGURE 9-11.** More recently, we have seen the accumulation of data suggesting that estrogen can reduce the risk of nonvertebral fracture. Komulainen *et al.* [23] showed that there were fewer nonvertebral fractures occurring over 5 years in early postmenopausal women ($n$ = 232) treated with hormone replacement therapy (HRT).

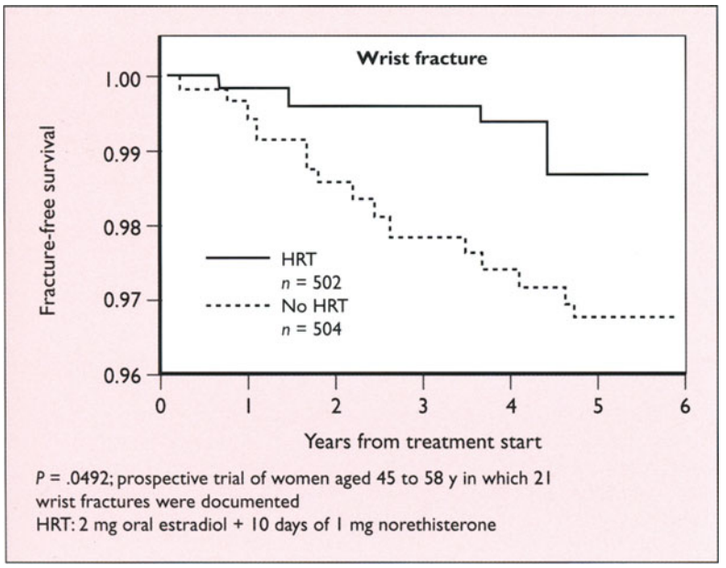


**FIGURE 9-12.** The Danish Osteoporosis Prevention Study was the first large randomized prospective study that assessed the preventive effects of hormone replacement therapy (HRT) on fracture rates in 2016 recently postmenopausal women aged 45 to 58 years. After 5 years of treatment, the women receiving HRT experienced statistically significant reductions in the relative risk of Colles' fracture (RR, 0.45; 95% CI, 0.22–0.90) and borderline statistically significant reductions in overall nonvertebral fracture risk (RR, 0.73; 95% CI, 0.50–1.05). However, when the analysis was restricted to women who adhered to the regimen, significant risk reductions were seen in overall fracture risk (RR, 0.61; 95% CI, 0.39–0.97) and in the risk of Colles' fracture (RR, 0.24; 95% CI, 0.09–0.69). (*Adapted from* Mosekilde *et al.* [24].)

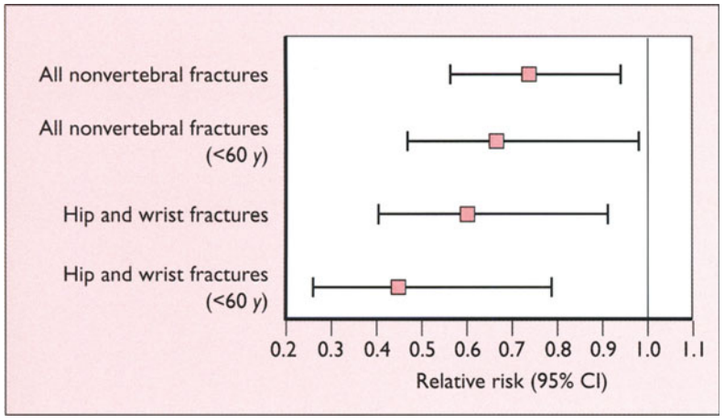


**FIGURE 9-13.** These results are from recent meta-analysis of all randomized trials of hormone replacement therapy (HRT) that have reported or collected information on nonvertebral fracture, although most did not focus on fracture prevention. This meta-analysis reported a 27% reduction in the relative risk of nonvertebral fractures (RR, 0.73%; 95% CI, 0.56–0.94). Greater reductions in relative risk of nonvertebral fracture were observed in women with a mean age younger than 60 years (RR, 0.67%; 95% CI, 0.46–0.98). In women 60 years of age and older, HRT appeared to have a lesser effect on nonvertebral fracture (RR, 0.88%; 95% CI, 0.71–1.08).

The effectiveness of HRT appeared more marked for hip and wrist fractures alone (RR, 0.60; 95% CI, 0.40–0.91), especially for women younger than 60 years of age (RR, 0.45; 95% CI, 0.26–0.79). This meta-analysis confirmed the significant benefits of HRT in preventing nonvertebral fractures, particularly in younger women. Initiating therapy early in menopause may be necessary to maximize the benefit of HRT in preventing fracture. (*Adapted from* Torgerson and Bell-Syer [25].)

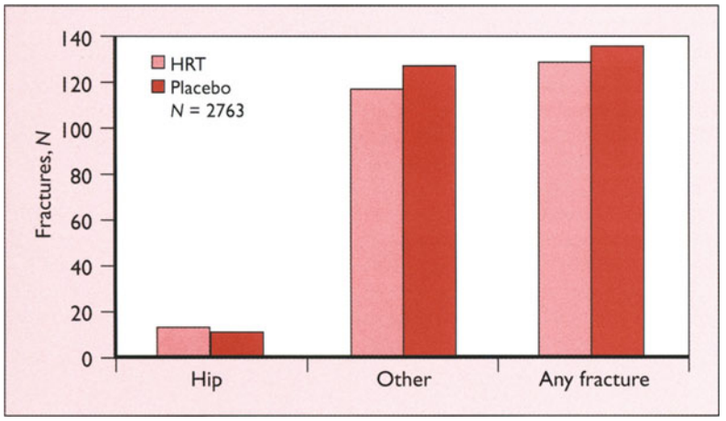


**FIGURE 9-14.** The Heart Estrogen/progestin Replacement Study, a study evaluating hormone replacement (HRT) for secondary prevention of heart disease, could find no evidence of fracture reduction in 2763 women with established coronary heart disease. The osteoporosis status of the majority of these women was unknown and they were followed for a median of 5.3 years. Results indicated that HRT produced an increased risk of coronary heart disease, particularly in the first year, and no overall reduction in the risk of cardiovascular disease. Moreover, there was no reduction in the risk of any clinical fracture (spine or hip) or of all fractures in women receiving HRT versus those receiving placebo. (*Adapted from* Hulley *et al.* [26].)

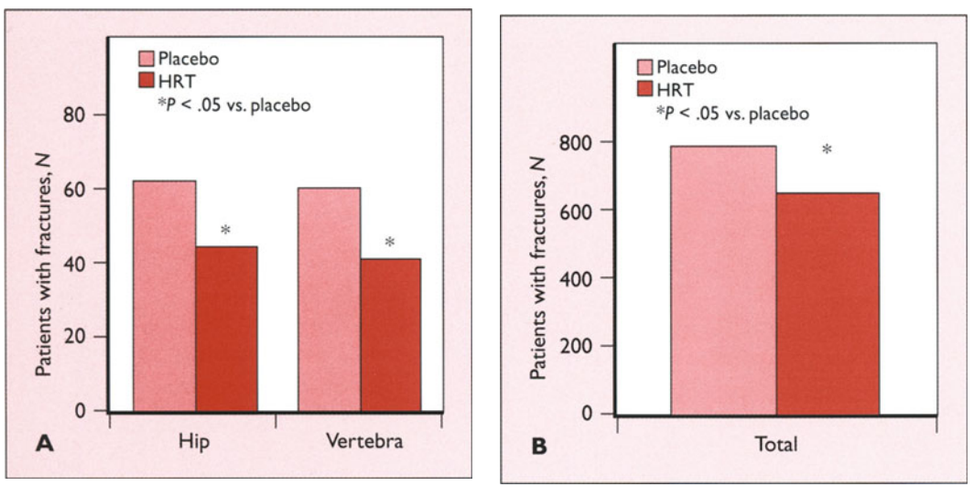


**FIGURE 9-15.** The largest clinical trial of hormone replacement therapy (HRT) ever done is the HRT portion of the Women's Health Initiative [27], a large complex clinical trial evaluating HRT, estrogen, low-fat diet, and calcium and vitamin D supplementation. **A** and **B**, In the HRT arm of the study, some 16,600 postmenopausal women were randomized to receive placebo or HRT—conjugated equine estrogen 0.625 mg/d + medroxyprogesterone acetate 2.5 mg/d. The multiple outcomes evaluated included heart disease, stroke, venous thromboembolism, and breast, uterine, and colon cancer as well as fractures, which did not include those of the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae. Such fractures are more difficult to confirm or are often not osteoporotic in etiology.

Forty-four patients (0.10%) receiving HRT experienced hip fractures, compared with 62 receiving placebo (0.15%); 41 patients (0.09%) receiving HRT and 60 patients (0.15%) receiving placebo experienced clinical vertebral fractures; and 650 women (1.47%) receiving HRT and 780 women (1.91%) receiving placebo experienced other types of fractures. The use of HRT reduced the rates of observed hip and clinical vertebral fractures by 34% and reduced the risk of all other fractures compared with placebo by 24%. This reduction was nominally significant for all fractures. In terms of absolute risk, 10,000 women taking HRT compared with placebo might experience five fewer hip fractures over 1 year. These data confirm the overwhelming body of data on the biologic impact of estrogen deficiency on the skeleton, the previous small clinical trials and the observational studies making the Heart and Estrogen/progestin Replacement Study trial the one outstanding negative study of estrogen and fracture outcomes.

**WHI RESULTS: ABSOLUTE AND RELATIVE RISK OR BENEFIT OF CEE/MPA**

| Health Event | Overall Hazard Ratio | Confidence Interval Nominal 95% | Confidence Interval Adjusted 95% | Increased Absolute Risk per 10,000 Women/Y | Increased Absolute Benefit per 10,000 Women/Y |
|---|---|---|---|---|---|
| CHD | 1.29 | 1.02–1.63* | 0.85–1.97 | 7 | |
| Strokes | 1.41 | 1.07–1.85* | 0.86–2.31 | 8 | |
| Breast cancer | 1.26 | 1.00–1.59 | 0.83–1.92 | 8 | |
| VTED | 2.11 | 1.58–2.82* | 1.26–3.55* | 18 | |
| Colorectal cancer | 0.63 | 0.43–0.92* | 0.32–1.24 | | 6 |
| Hip fractures | 0.66 | 0.45–0.98* | 0.33–1.33 | | 5 |
| Total fractures | 0.76 | 0.69–0.85* | 0.63–0.92* | | 44 |

**FIGURE 9-16.** For the clinical outcomes listed here, the overall hazard ratios (HRs) at 5.2 years for conjugated equine estrogen (CEE)/medroxyprogesterone acetate (MPA) users versus placebo are shown in the second column from the left. For each of these ratios, two different confidence intervals (CIs) were calculated, nominal and adjusted (based on multiple comparisons), and the intervals that reached statistical significance, that is, those that did not cross 1.0, are indicated with an asterisk (*). Reporting on both types of CIs in the same publication is rare, as they tend to make interpretation of the data difficult. The nominal CI for coronary heart disease (CHD) and the adjusted CI for stroke indicate statistically significant increases in risk among CEE/MPA users. Both the nominal and the adjusted CIs for venous thromboembolic disease (VTED—the combination of deep vein thrombosis and pulmonary embolism) indicate a statistically significant, more than twofold increase in risk among CEE/MPA users. Both the nominal and the adjusted CIs for total fractures indicate statistically significant decreased risk among CEE/MPA users. The nominal CIs for colorectal cancer and hip fracture indicate statistically significant decreases in risk among CEE/MPA users [27].

The risk of breast cancer was increased by 26%, just missing statistical significance. The absolute excess risk or benefit attributable to CEE/MPA was low. The Women's Health Initiative (WHI) findings predict that over 1 year, 10,000 women taking CEE/MPA, compared with placebo, might be expected to experience 7 more CHD events, 8 more strokes, 8 more invasive breast cancers, 18 more thromboembolic events, 6 fewer colorectal cancers, 5 fewer hip fractures, and 44 fewer total fractures. All these numbers must be multiplied by years of use, however, in order to fully estimate the absolute risk of all these diseases.

## Importance of Estrogen in Men

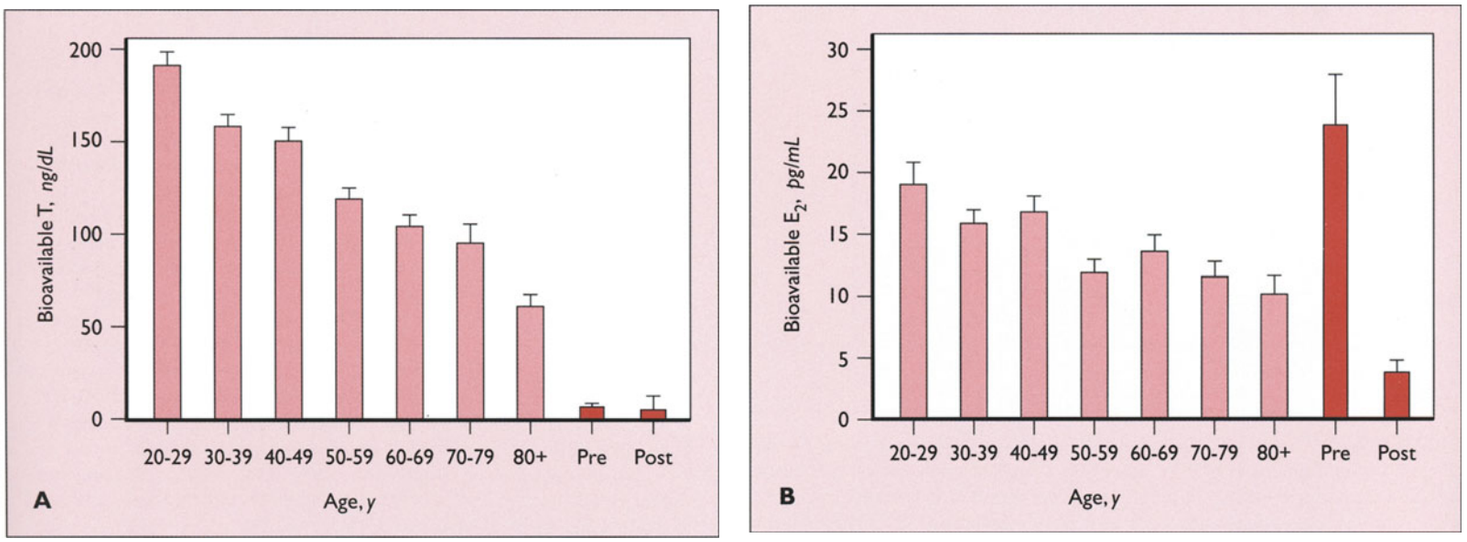


**FIGURE 9-17.** In a population-based, age-stratified sample of 346 men, aged 23 to 90 years, bioavailable (non–sex-hormone–binding globulin band) testosterone (T) (**A**) and estrogen ($E_2$) (**B**) decreased by 69% and 47%, respectively. While the level of bioavailable testosterone was always higher in men than in a parallel group of women, in fact the level of bioavailable estrogen was higher in even the oldest men [28–30], compared with postmenopausal women. Levels of both bioavailable testosterone and estrogen correlated positively with bone mineral density (BMD) at all skeletal sites and negatively with urine N-telopeptide excretion. Serum level of bioavailable estrogen was a stronger independent predictor of BMD in these men. Pre—premenopausal women; Post—postmenopausal women. (*Adapted from* Khosla *et al.* [28].)

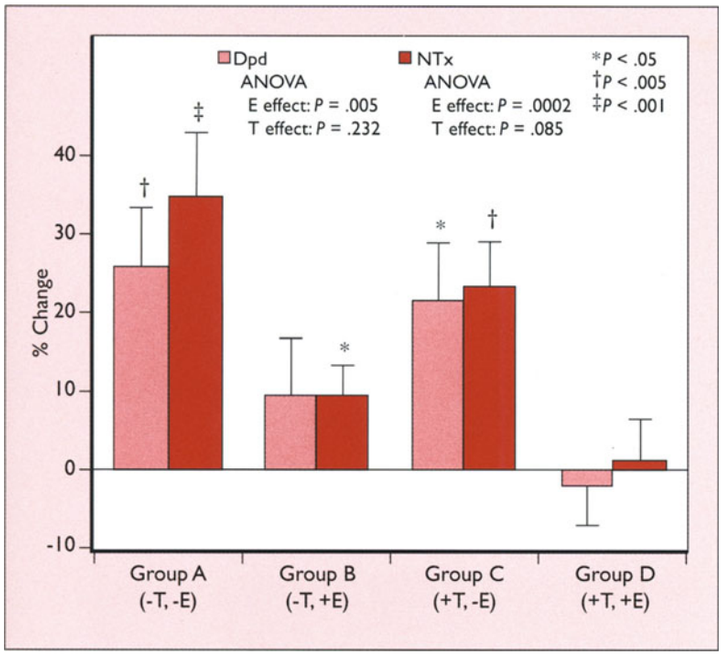


**FIGURE 9-18.** In this study, 59 men of mean age 68 years were treated with gonadotropin-releasing hormone agonist therapy to induce testosterone deficiency and started on an aromatase inhibitor to block production of estrogen from androgen. As expected in group A, in which no HRT or testosterone was given, urinary deoxypyridinoline (Dpd) and N-telopeptide (NTx) increased 26% to 35%. Testosterone administration (Group C) reduced the increase in bone resorption, but was not as potent as estrogen administration (Group B), which accounted for about 65% of the effect of hormonal deficiency on bone resorption. The combination of both testosterone (T) and estrogen (E) replacement therapy was effective in returning bone resorption to baseline levels. These findings extend other observations and suggest that estrogen may be even more important than testosterone in the regulation of bone turnover and the maintenance of skeletal health in older men. (*Adapted from* Palahati-Nini *et al.* [31].)

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10

# OSTEOPOROSIS IN MEN

*Eric S. Orwoll and Robert F. Klein*

Although long recognized as a disease of women, osteoporosis also has an important impact on men. Recognition of the magnitude of the problem of osteoporosis in men has only recently occurred, and few data exist concerning its character and etiology. Epidemiologic data indicate that one in four 50-year-old white men will experience an osteoporotic fracture during his remaining lifetime. Thus, osteoporosis in men represents a serious public health problem. Osteoporosis in men is similar in many ways to that in women but exhibits unique features and clinical challenges.

Bone mass declines with advancing age regardless of gender, leading to an increased risk of skeletal fracture. In many ways, the skeletal changes in men parallel those in women, but, several differences probably influence the presentation of this disorder in men. During puberty, diverging growth trends result in obvious gender differences in peak skeletal development. Virtually all skeletal dimensions in men are larger than those in women. As a result, total body bone mineral is approximately 20% greater in men than in women. The larger size of male bones adds greatly to their strength, and the gender differences in peak bone mass and size underlie, in part, the differences in fracture patterns between men and women that emerge later in life. Changes in bone mineral density (BMD) are not particularly different between men and women, but differences in the nature of structural changes with aging between the genders may have important biomechanical consequences, as load bearing of bone specimens appears to be better preserved in men.

The incidence of skeletal fractures is biphasic in men. Early in life, fracture occurrence is actually higher in men than in women, probably as the result of serious trauma. At about 40 to 50 years of age, the trend reverses and fractures become more common in women. Later, the incidence of fractures increases in men older than 60 years of age, reflecting an increasing prevalence of skeletal fragility. The cause of age-related bone loss in men is unclear. Both increased osteoclastic and reduced osteoblastic activities have been postulated to occur, but the relative participation of each is unknown. Dietary calcium insufficiency and alterations in vitamin D metabolism, an age-related decrease in sex steroid levels, and relative inactivity all may play a role. Additional conditions may secondarily accelerate bone loss in men, including alcohol and tobacco abuse, glucocorticoid therapy, hypogonadism, and hypercalciuria. The prevalence of these conditions in men with osteoporosis is unclear. Various biochemical markers of bone remodeling have been related to BMD in healthy men and osteoporotic men. Their use as diagnostic tools, however, requires further investigation.

In men who present with findings suggestive of the presence of reduced bone mass (*ie*, low-trauma fractures, radiographic criteria of osteopenia, or conditions associated with bone loss), measurement of bone mass (or density) should be strongly considered. Bone mass determinations in men can be used to confirm the diagnosis of low bone mass, gauge its severity, and serve as a baseline from which to judge the progression or improvement of disease. If a man is found to be osteopenic, an evaluation should be performed to determine with reasonable certainty the cause of the disorder. The history, physical examination, and routine laboratory studies can be helpful in directing the focus of the evaluation of a man with low bone mass. When no clear pathophysiology is identified, it is appropriate to be aggressive diagnostically, primarily because the potential for occult secondary causes of osteoporosis may be higher in men.

Treatment options for men with osteoporosis include agents that slow bone resorption or augment bone formation. Any of the medical conditions associated with excessive bone loss should be specifically addressed to prevent and treat osteoporosis. The effectiveness of therapies for osteoporosis in men has recently been documented. Bisphosphonates are clearly useful in preventing the bone loss that occurs with glucocorticoid use, and alendronate increases bone density and reduces vertebral fractures in men with idiopathic osteoporosis. Parathyroid hormone therapy also increases bone mineral density in men with idiopathic osteoporosis, and the rate of vertebral fracture is reduced to an extent similar to that observed in osteoporotic postmenopausal women treated with parathyroid hormone. Importantly, alendronate and parathyroid hormone treatments appear to be equally effective in men with normal and low testosterone levels.

In summary, osteoporosis in men is a common disorder, the incidence of which is increasing. Despite new developments in the care of men with osteoporosis, it appears that affected men are rarely detected and treated. Osteoporosis in men presents a unique array of scientific challenges and opportunities and deserves the same vigorous evaluation as that applied to postmenopausal osteoporosis. Additional efforts are needed to effectively prevent osteoporotic fractures in men.

# Incidence and Risk

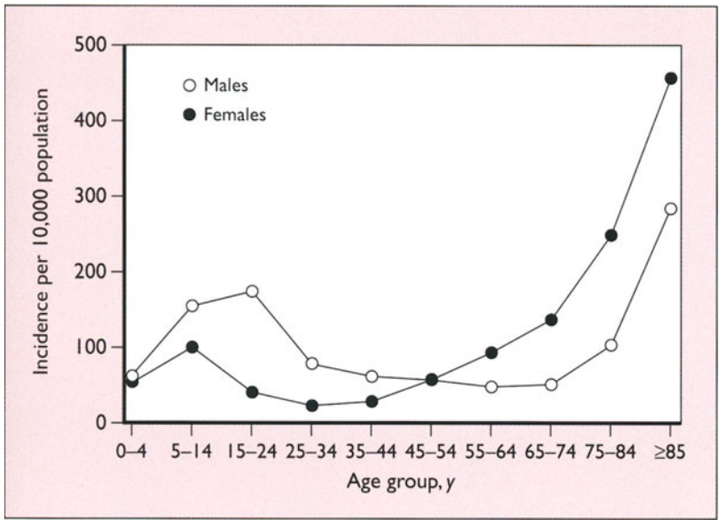



**FIGURE 10-1.** Fracture incidence rate by age group and gender. In women, the relationships between fractures and bone mass, the propensity for falls, and other risk factors have become increasingly well defined. In men, less information is available regarding the causation of fracture; hence, the current understanding of osteoporosis epidemiology is limited primarily to fracture patterns [1]. From adolescence through midlife, the incidence of all fractures is higher in men than in women, and the personal and economic impact (in terms of hospitalizations and lost work days) of these early-life fractures is enormous. Despite the importance of early-life fractures in men, little has been done to elucidate their cause. Many result from serious trauma, but to some extent relative bone fragility may also contribute to fracture risk during this period. For instance, men who have sustained traumatic tibial [2] or forearm fractures [3] in early midlife are at much greater risk for hip fracture later in life. At about 40 to 50 years of age, a reversal of this trend occurs, with fractures in general and those of the pelvis, humerus, forearm, and femur in particular becoming much more common in women. However, the incidence of fractures resulting from minimal to moderate trauma (particularly the hip and spine) also increases rapidly with aging in men and reflects an increasing prevalence of skeletal fragility.

**RISK OF AN OSTEOPOROTIC FRACTURE FROM AGE 50 YEARS**

**Estimated Lifetime Fracture Risk in % (95% Confidence Intervals) in White Women and Men at the Age of 50 Years**

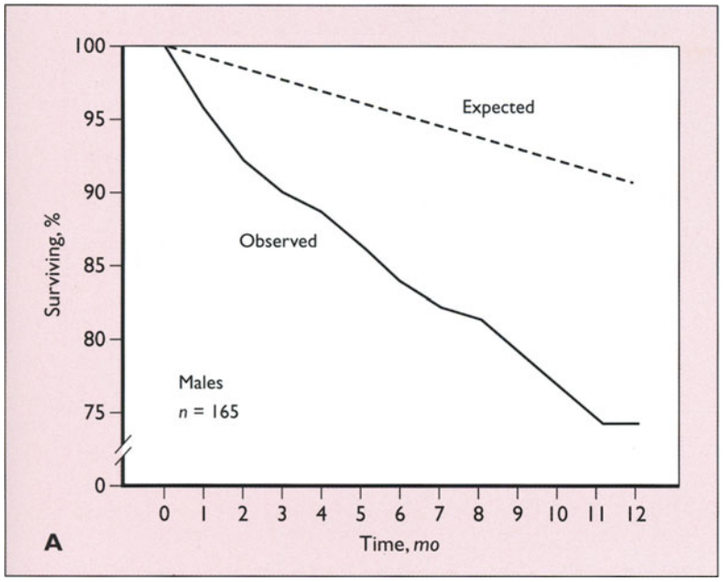
| Fracture Site | Women | Men |
|---|---|---|
| Proximal femur | 17.5 (16.8–18.2) | 6.0 (5.6–6.5) |
| Vertebral* | 15.6 (14.8–16.3) | 5.0 (4.6–5.4) |
| Distal forearm | 16.0 (15.7–16.7) | 2.5 (2.2–3.1) |
| Any of the above | 39.7 (38.7–40.6) | 13.1 (12.4–13.7) |

**Re-evaluation of Estimated Lifetime Hip Fracture Risk (%) in White Women and Men at the Age of 50 Years†**

| | Women | Men |
|---|---|---|
| Current average life expectancy | 13.9 | 4.9 |
| Using present mortality rates | 19.5 | 8.1 |
| Using predicted mortality rates | 22.7 | 11.1 |

**Clinically diagnosed fractures (from Melton et al. [1991]).*
*†From Oden et al. (1998).*

**FIGURE 10-2.** Risk of an osteoporotic fracture from age 50 years. The lifetime risk of sustaining an osteoporotic fracture of the hip, spine, or wrist for a 50-year-old man is about one third of that for a woman (13% *vs* 39%) [4]. The incidence of hip fracture increases exponentially in men with aging, as it does in women. However, the age at which the increase begins is slightly greater (approximately 5–10 years) in men. There are fewer older men than women; thus, the absolute number of hip fractures tends to be proportionately less in men, but, it is estimated that about 30% of the two million hip fractures worldwide occur in men. Oden *et al.* [5] re-examined the question of lifetime hip fracture risk at age 50 years in men and women. They noted that it is probably more appropriate to use mortality rates at age 50 years (rather than overall life expectancy) to calculate risks, and when that approach was used the risk of hip fracture was considerably higher. In addition, when they projected a lower mortality rate in the future (since mortality rates are falling), the expected hip fracture risk was even more dramatic in both sexes. Vertebral fracture also is an important sequela of osteoporosis in men. As in women, the presence of vertebral fracture in men is associated with loss of height, kyphosis, increased risk of other fractures, and increased disability. Previously considered uncommon in men in the United States, recent information suggests that the incidence of osteoporotic vertebral fracture in men is about half that in women [6]. Vertebral bone mineral density values are reduced in men with vertebral fractures compared with those in the control group without fracture, indicating that vertebral fracture in men is not merely the result of a higher rate of trauma but is also related to the presence of low bone mass. Fractures occur primarily in low thoracic vertebrae in men but are found at all levels. Most fractures are anterior compression in type, with vertebral crush fractures occurring less frequently than is reported in women. Vertebral epiphysitis (Scheuermann disease) is an uncommon cause of significant vertebral deformity in men. The incidence of forearm fractures increases markedly in aging women but remains relatively stable throughout life in men. (*Adapted from* Melton *et al.* [4].)



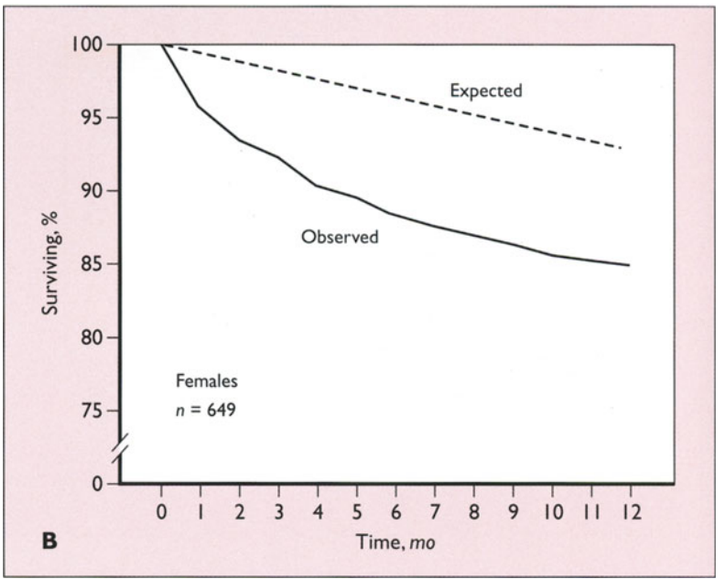




**FIGURE 10-3.** Survival of women and men after hip fracture. Men who present with hip fracture usually are elderly and fragile and have multiple pre-existing medical conditions [7]. In men (**A**), hip fracture results in significant functional decline and a threefold higher postfracture mortality rate compared with aged-matched women (**B**) [8]. These facts highlight the need to identify men with osteoporosis in the community and find effective strategies for preventing hip fracture. (*Adapted from* Diamond *et al.* [7] and Magaziner *et al.* [8].)

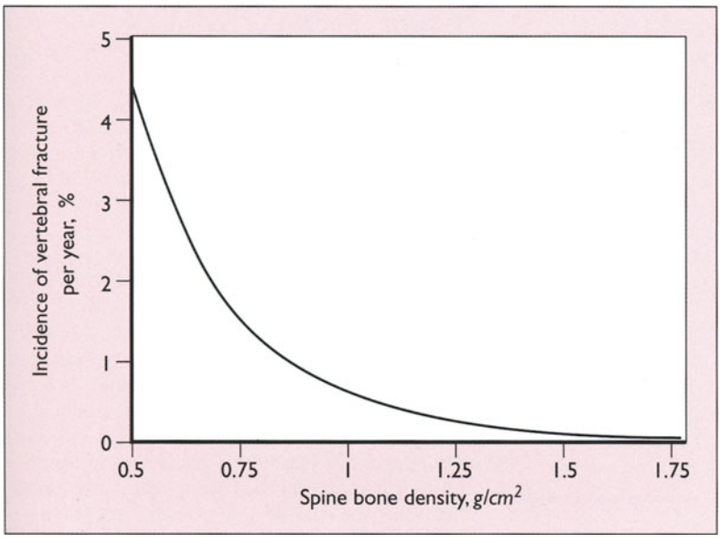



**FIGURE 10-4.** Fracture occurrence in men with different bone densities. There is substantial evidence that in a postmenopausal and elderly white woman, low bone mass is associated with an increased risk of fracture. A single bone mineral density (BMD) measurement at any commonly assessed appendicular or axial site predicts the overall risk of fractures in both sexes. Although data are less available in men, accumulating evidence documents an inverse relationship of bone mass to fracture. Shown here are the results of a longitudinal study investigating the predictive value of baseline spinal BMD measurement for vertebral fracture occurrence in a large cohort of elderly European men [9]. As in women, the gradient of increasing fracture risk with decreasing bone mass in men appears to be continuous, with no true biologic threshold. Based on available data, the fracture risk increases about 1.4-fold (95% CI, 1.1–1.9) for every 0.1 g/cm$^2$ reduction in spinal BMD, which is similar to the risk increase in women.

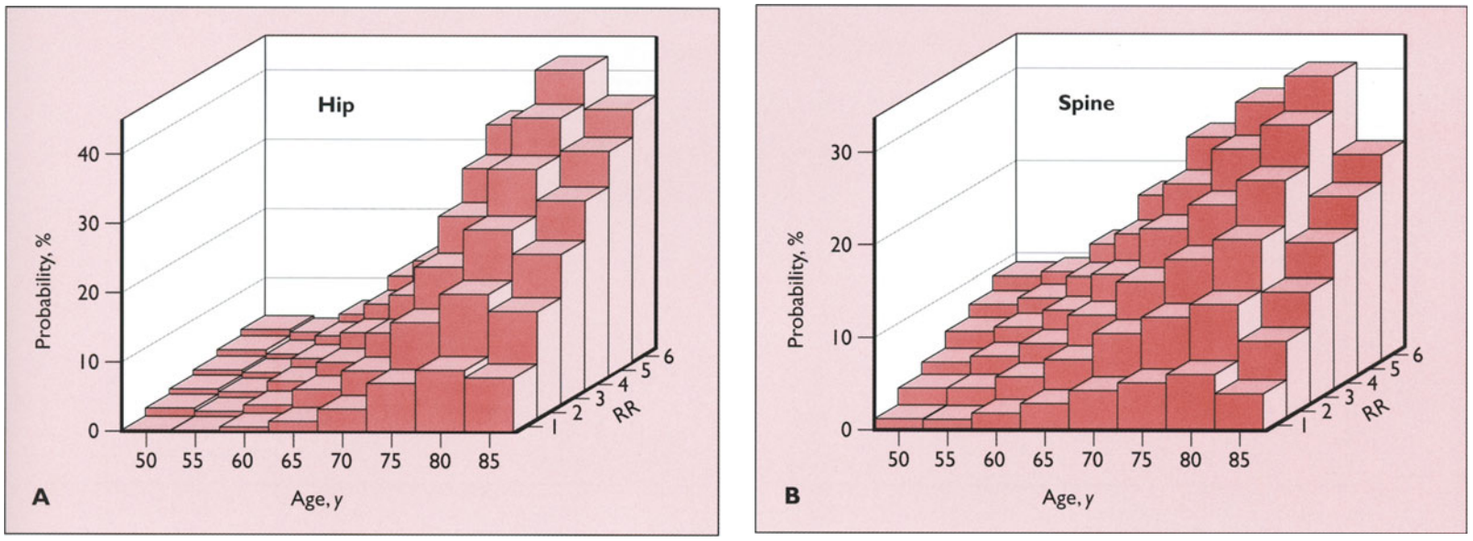



**FIGURE 10-5.** **A** and **B**, The relationship between the absolute risk of spine and hip fracture, increasing age, and increasing relative risk in men. The absolute risk of hip and spine fracture is heavily dependent on the subject's age and relative risk of fracture. Although researchers assign the degree to which relative risk changes in men as the clinical situation varies (*eg*, with smoking or positive family history), it is useful to observe how much absolute risk is affected by changes in age and relative risk. In these studies, data from the Swedish population were used to model these relationships. In fact, the 10-year risk of fractures was very high in older men with higher relative risk [10]. In this model of a 75-year-old man with a relative risk of 3 (*eg*, low bone mineral density plus increased risk of falls and a positive family history), the 10-year risk of hip or vertebral fracture was 20% to 30%.

**FACTORS ASSOCIATED WITH HIP FRACTURES IN MEN**

| Metabolic Disorders | Disorders of Movement and Balance |
|---|---|
| Thyroidectomy | Hemiparesis/hemiplegia |
| Gastrectomy | Parkinsonism |
| Pernicious anemia | Other neurologic diseases |
| Chronic respiratory diseases | Vertigo |
| Lean body mass | Alcoholism |
| | Anemia |
| | Blindness |
| | Use of cane or walker |
| | Inactivity |
| | Dementia |

**FIGURE 10-6.** Factors associated with hip fractures in men. As in women, there is overlap of bone density in men with fractures and the control group without fracture, indicating that bone density is not the sole determinant of osteoporotic fracture risk. Fracture is a somewhat chance event, and the propensity to fall is an important variable. In men, few prospective data exist that directly relate fall propensity to subsequent fractures, but a variety of factors indirectly related to the risk of falling have been related to hip fracture. Many of these differences suggest a body habitus and lifestyle more conducive to falls and injury, as well as the possibility of other interacting risk factors (nutritional deficiencies and comorbidities). In this retrospective study of conditions associated with hip fracture, increased risk was related to increased age, leanness, increased height, a history of previous fracture, and osteoporosis. In addition, a number of metabolic and neurologic diagnoses were more often found in the medical histories of men who experienced a hip fracture [11].

# Bone Mass Density and Structure

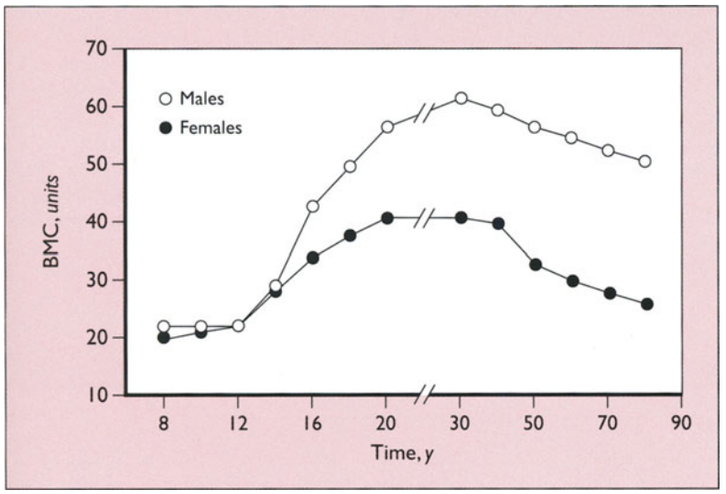



**FIGURE 10-7.** Changes in bone mass with growth and aging in men and women. Both men and women exhibit a dramatic increase in bone mass that begins during adolescence and is almost complete when puberty ends. A lifetime peak is reached in both men and women at about 20 to 30 years. By the fourth or fifth decade, men and women begin an age-related process of gradual bone loss that continues throughout the remainder of life. This age-related decrease in bone mass results from an excess of bone resorption over bone formation, the causes of which are not well understood. Women experience an accelerated phase of bone loss lasting 5 to 15 years that is the result of the relatively abrupt decline in gonadal function occurring with menopause. In contrast with the clearly demarcated event of menopause in women, the reproductive changes that take place in men as they age are more subtle. Acceleration occurs in the rate of bone loss in elderly men (>50 years), which most likely is also the result of reductions in sex steroid levels. At any given time, bone mass depends on the peak bone mass achieved in adolescence and subsequent bone loss. BMC—bone mineral content. (*Adapted from* Nevitt [12].)

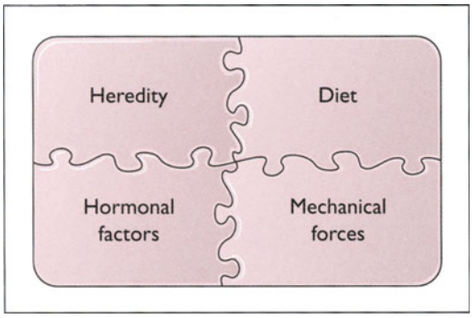
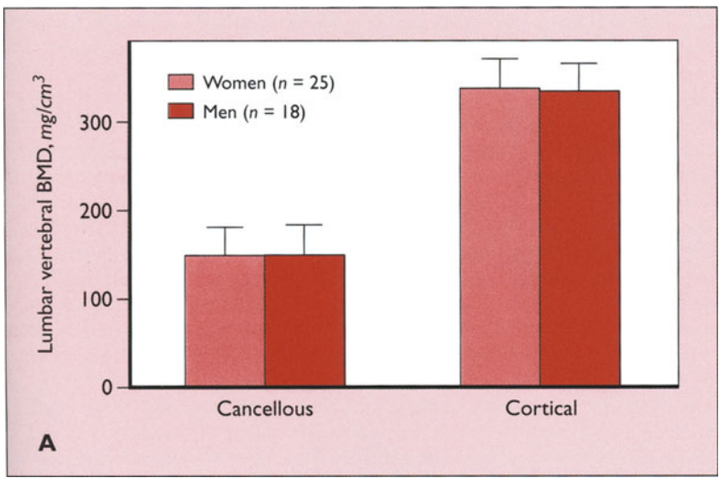



**FIGURE 10-8.** Determinants of peak bone mass in men. Peak bone mass is the major determinant of osteoporotic fracture risk up to the age of approximately 60 to 65 years, when factors such as age-related bone loss become relatively more important. Hence, the failure to achieve optimal peak bone mass is an important pathogenetic mechanism in osteoporosis in both men and women. Although comparatively little attention has been paid over the years to the determinants of peak bone mass in men, heredity, dietary components (calcium and protein), endocrine factors (sex steroids, calcitriol, and insulin-like growth factor-I), and mechanical forces (physical activity and body weight) all have been shown to have an influence. As in women, the most prominent determinant appears to be genetically related, but the precise genes involved remain to be elucidated.



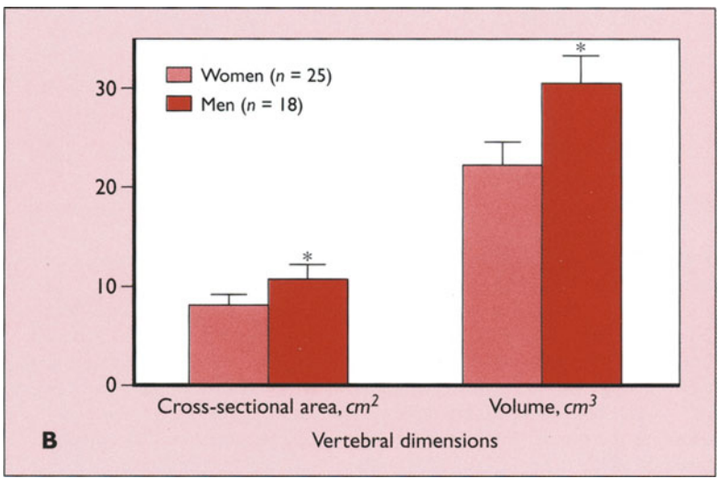




**FIGURE 10-9.** Gender differences in bone size and density. In early childhood, few discernible differences can be observed between the skeletons of boys and girls; however, as the skeleton matures during puberty, obvious sexual differences in bone morphology emerge [13–15]. Most skeletal dimensions in men are larger than those in women. As a result, total body bone mineral is greater in men (2300–2700 g in young women vs 3100–3500 g in young men). Although maximal adult bone mineral density (BMD) is also frequently reported to be greater in men, this result is primarily an artifact of the measurement methods used. For instance, adult vertebral BMD determined by quantitative computed tomography, which is a true volumetric assessment, is alike in men and women (**A**). Whereas vertebral density by measures of area (eg, dual-photon absorptiometry or dual-energy x-ray absorptiometry) appears to reach slightly higher levels in men, this apparent advantage disappears (or is even slightly reversed) once those values are corrected for differences in vertebral dimensions. The adolescent development of adult bone mass depends on changes in both density and size, with increases in size being quantitatively much more important. From the time of puberty on, mean vertebral cross-sectional area is 15% to 25% greater in men and tubular bones exhibit greater total and cortical widths in early adulthood (**B**). The larger size of bones in men adds greatly to their strength, and the sex differences in peak bone mass and, in part, size underlie the differences in fracture patterns that emerge later in life. (*Adapted from* Gilsanz *et al.* [15].)

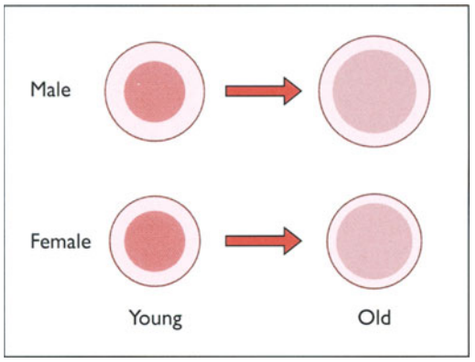



**FIGURE 10-10.** Gender differences in age-related changes in cortical bone. Bone loss occurs with aging in men as it does in women; however, gender differences in the pattern of age-related bone loss affect eventual fracture risk. Both men and women experience an increase in porosity, although the rate is somewhat slower in men. This increase results in a reduction in density and mechanical strength, thereby increasing fracture risk. However, the decrease in mass is compensated, to some extent, by changes in cortical dimensions. An age-related increase in total cortical width exists in men and women. This change is beneficial because fracture resistance is dependent on geometry. The rate of cortical loss is very similar in both men and women; however, periosteal apposition is somewhat greater in men and endocortical loss somewhat less, mitigating the loss of thickness and overall mass [16,17]. The typical pattern of age-related change observed in cross sections of long bones is depicted. Men and women experience cortical thinning; however, men undergo compensatory increases in section breadth to a greater degree than do women. The tensile resistance of a long bone to fracture is exponentially related to its diameter; thus, the morphologic changes are in accord with the fracture patterns observed in the elderly, in whom the rate of appendicular fractures is less in men than in women. (*Adapted from* Beck *et al.* [16].)

# Causes

**DIFFERENTIAL DIAGNOSIS OF OSTEOPOROSIS IN MEN**

Primary
- Senile
- Idiopathic

Secondary
- Hypogonadism
- Glucocorticoid excess
- Alcoholism
- Gastrointestinal disorders
- Hypercalciuria
- Smoking
- Anticonvulsants
- Thyrotoxicosis
- Immobilization
- Osteogenesis imperfecta
- Homocystinuria
- Systemic mastocytosis
- Neoplastic diseases
- Rheumatoid arthritis

**FIGURE 10-11.** Osteoporosis in men is a heterogeneous condition, encompassing a wide variety of causes and clinical presentations. In practice, it is not uncommon to identify several potential explanations for bone loss and fractures in a single patient. The principal conditions found in men with reduced bone mass are presented. Prominent are glucocorticoid excess, hypogonadism, alcoholism, gastrectomy and other gastrointestinal disorders, and hypercalciuria. Similar attempts to examine the contributing factors in women with osteoporosis suggest that the spectrum of disorders is somewhat different; however, glucocorticoid excess, premature hypogonadism, and gastrointestinal disorders are prominent in women as well. It has been suggested that "secondary" osteoporosis occurs more frequently in men than in women. However, in other objective evaluations, the proportion of women with major illnesses contributing to the development of bone disease is very similar to that observed in men with osteoporosis.

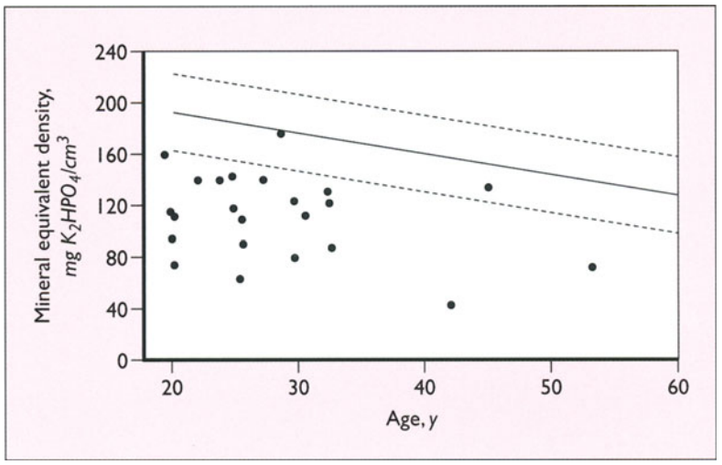



**FIGURE 10-12.** Hypogonadism and osteopenia in men. Puberty is very important in skeletal maturation; thus, disorders of puberty have the potential to impair peak bone mass development and thus influence fracture risk throughout adulthood. Supporting the importance of androgen action in the achievement of peak bone mass in men is the fact that genetic males with complete androgen insensitivity (testicular feminization) experience increased pubertal growth but achieve a bone mass typical of genetic women [18]. Reduced bone mass is found in men who experienced an abnormal puberty (Klinefelter and Kallmann syndromes), and even constitutionally delayed puberty is associated with permanent reductions in bone density. The results of a study by Finkelstein *et al.* [19] are shown, who examined spinal trabecular bone mineral density in 23 men with idiopathic hypogonadotrophic hypogonadism. Androgens also appear to be essential for the maintenance of bone mass in adult men because the development of hypogonadism in mature men is associated with low bone mass. Hypogonadism is present in as many as one third of men evaluated for vertebral fractures and osteoporosis, and hip fractures in elderly men apparently occur more commonly in the setting of hypogonadism. Reduced bone mass and fractures are associated with many forms of hypogonadism, including castration, hyperprolactinemia, anorexia, and hemochromatosis. The degree of reduction in bone density has been correlated with levels of serum testosterone in some series; however, in other studies, no association between the two variables is apparent. A threshold level of serum testosterone may exist below which skeletal health is impaired. At present, however, it is not possible to establish that hypothesis. (*Adapted from* Finkelstein *et al.* [19].)

**CHANGES IN BONE METABOLISM AFTER CASTRATION IN MEN**

| Parameter | Normal | Orchidectomy |
|---|---|---|
| Serum testosterone, *nmol/L* | 19.4 ± 7.6 | 1.6 ± 1.1* |
| Bone formation: | | |
| Serum osteocalcin, *mg/L* | 5.0 ± 1.6 | 12.1 ± 2.8* |
| Bone-specific alkaline phosphatase, *U/L* | 10.2 ± 2.3 | 20.4 ± 3.2* |
| Bone resorption: | | |
| Serum tartrate–resistant acid phosphatase, *U/L* | 4.33 ± 0.7 | 6.51 ± 1.0* |
| Urine hydroxyproline/creatinine, *mmol/mol* | 16.2 ± 2.8 | 27.7 ± 5.8* |
| Bone mineral density, $g/cm^2$ | 0.94 ± 0.14 | 0.83 ± 0.15* |

**FIGURE 10-13.** Effects of hypogonadism on male skeletal physiology. The histologic pattern of hypogonadal bone loss in adult men is inadequately described. A single report examines skeletal metabolism in the period immediately after gonadal failure. Stepan and Lachman [20] studied a small group of men in the years immediately after castration. These men were found to lose bone rapidly (approximately 7% per year) and to have clear biochemical indications of increased bone remodeling (increased serum osteocalcin levels and urinary hydroxyproline excretion). Unfortunately, no direct histomorphometric analyses were reported. Thus, no firm conclusions can be drawn concerning the remodeling defect induced by hypogonadism in men. The early increase in remodeling after androgen withdrawal, however, is consistent with recent reports of the biochemical and cellular events associated with androgen action (a suppression of cytokine production and osteoclast formation) [21]. *Significantly different from normal ($P < 0.01$). (*Adapted from* Stepan and Lachman [20].)

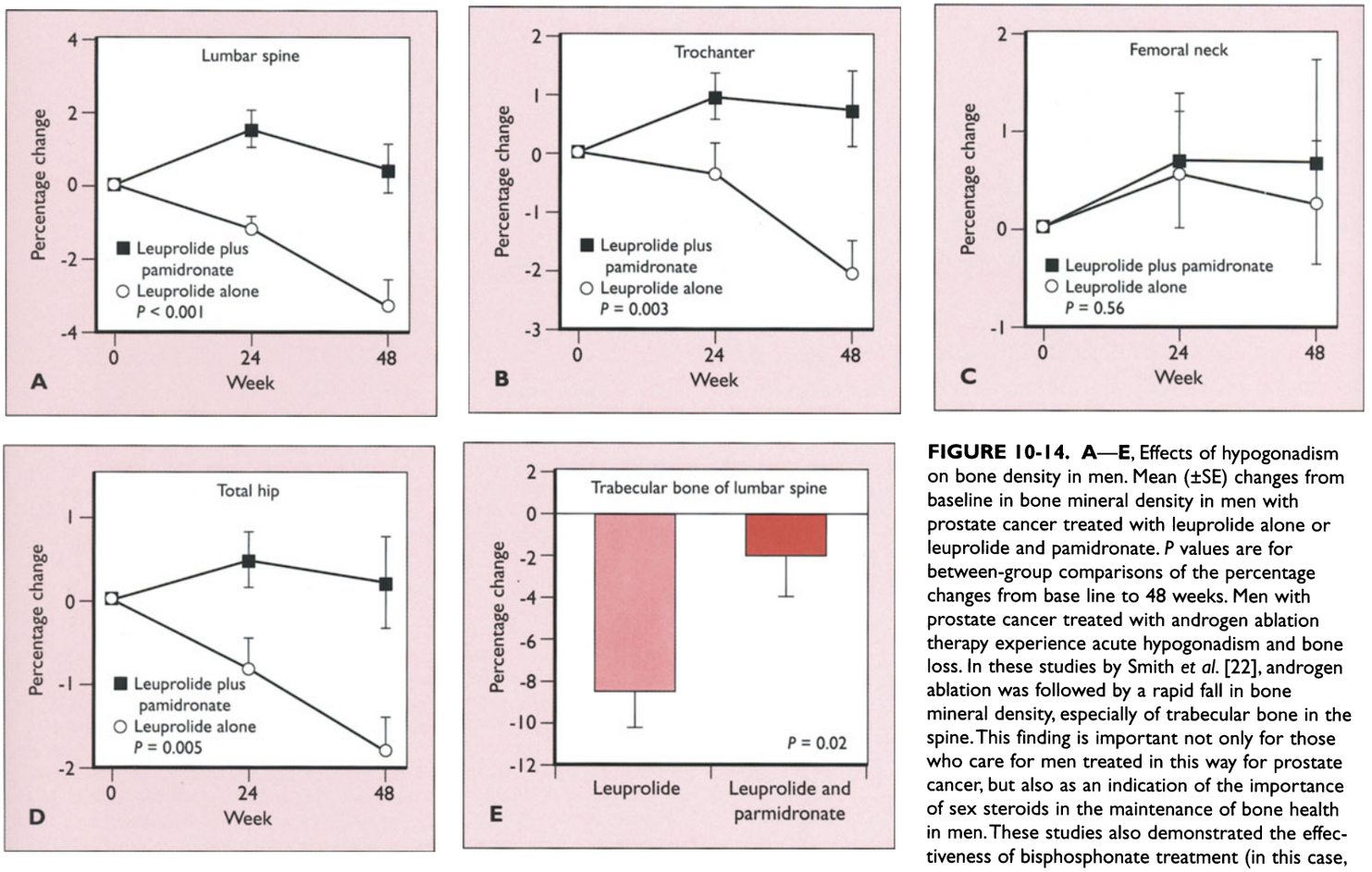



**FIGURE 10-14. A—E**, Effects of hypogonadism on bone density in men. Mean (±SE) changes from baseline in bone mineral density in men with prostate cancer treated with leuprolide alone or leuprolide and pamidronate. *P* values are for between-group comparisons of the percentage changes from base line to 48 weeks. Men with prostate cancer treated with androgen ablation therapy experience acute hypogonadism and bone loss. In these studies by Smith *et al.* [22], androgen ablation was followed by a rapid fall in bone mineral density, especially of trabecular bone in the spine. This finding is important not only for those who care for men treated in this way for prostate cancer, but also as an indication of the importance of sex steroids in the maintenance of bone health in men. These studies also demonstrated the effectiveness of bisphosphonate treatment (in this case, pamidronate) in the prevention of this form of bone loss.

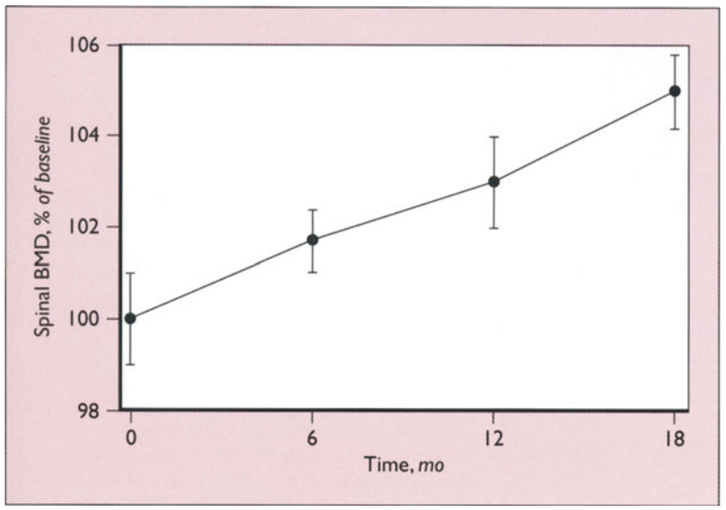
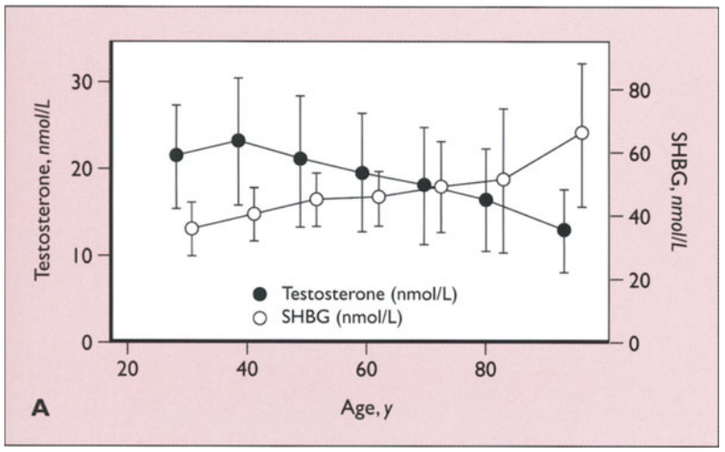



**FIGURE 10-15.** Impact of testosterone replacement therapy on bone mineral density (BMD) of hypogonadal men. The effectiveness of androgen replacement therapy in men with hypogonadism is unclear. Several reports have suggested that androgen replacement therapy may have beneficial effects on bone mass, at least in the short term. For example, in the study shown here, mean spinal BMD increased by 5% ($P < 0.001$) in a group of 36 men with acquired hypogonadism [23]. However, it is not certain that all men respond or whether other factors (*eg*, age and duration of hypogonadism) influence the success of treatment. Moreover, all studies that suggest a beneficial effect of androgen therapy are of short duration (1–5 years), and it is uncertain whether a sustained increase in bone mass occurs with therapy or whether bone mass ever reaches eugonadal levels. In addition, the minimal effective dose of androgen is not known. Of great importance is that the potential risks of androgen replacement therapy, particularly in the elderly, are uncertain in relation to the possible skeletal benefits to be gained. Nevertheless, the concern regarding bone loss and fractures should represent one of the indications for androgen therapy in gonadal failure.



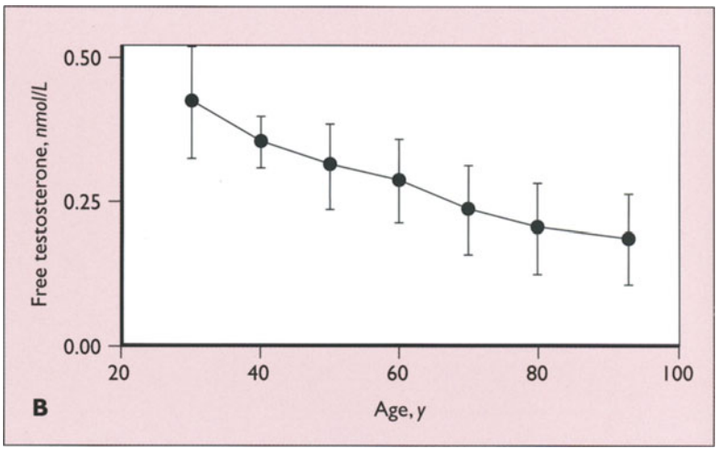




**FIGURE 10-16.** Testosterone levels decrease in aging men. The reproductive changes that take place in men as they age occur over a long period of time. These changes are more gradual than are the profound changes in gonadal function that occur in women at menopause. A decrease in total testosterone levels with aging has been reported in many, but not all, studies of normal healthy men (**A**). Most studies have reported a greater decrease in bioavailable testosterone, rather than in total testosterone concentrations, with age in men [24] (**B**). This fact is explained mainly by an age-related increase in the binding capacity of sex hormone–binding globulin (SHBG). The increase in SHBG is probably multifactorial in origin. Hepatic SHBG production is stimulated by estrogen and inhibited by insulin. Increased SHBG levels therefore may be the result of reduced insulin secretion and peripheral insulin sensitivity commonly observed in the elderly or a consequence of increased aromatization of androstenedione to estrone in peripheral (principally adipose) tissue known to occur in older men. Although great interindividual variability is observed in free testosterone levels with advancing age, it is estimated that nearly half of men older than 50 years of age have a free testosterone level below the lowest level seen in men younger than 40.

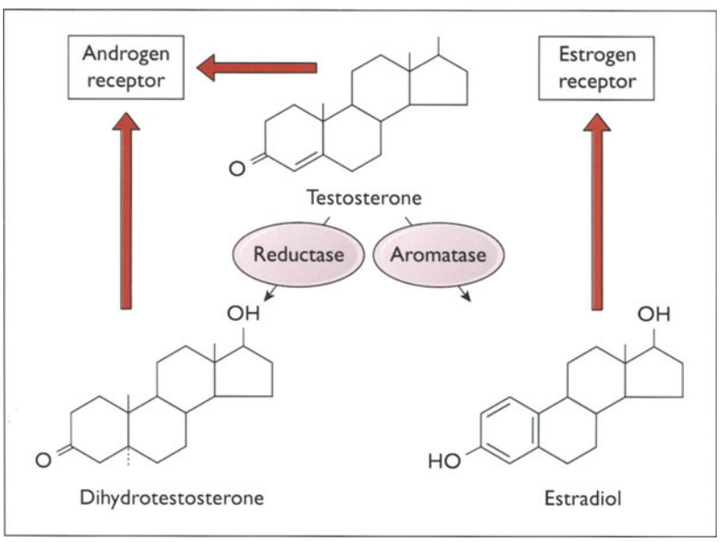



**FIGURE 10-17.** Metabolic conversion of testosterone. Once synthesized, testosterone can be converted either to dihydrotestosterone by 5α-reductase or to estrogen by aromatase, a member of the microsomal cytochrome P-450 group of enzymes. Both testosterone and dihydrotestosterone are capable of binding to and activating androgen receptors in osteoblasts. However, estrogen receptors are at least equally abundant in these cell lines and aromatase activity is also present in these cells. These observations raise the intriguing possibility that, in addition to androgens, estrogens are also of major importance for skeletal health in men. Recent case reports of osteoporosis in men with genetic disorders resulting in either defective aromatase activity or nonfunctioning estrogen receptors have called attention to the importance of estrogens in skeletal growth [25–28]. Convincing evidence that estrogen is essential for the establishment of peak bone mass in growing boys comes from the demonstration that although testosterone therapy produces no benefit, replacement of estrogen in men with inactivating aromatase gene mutations (and consequently lifelong estrogen deficiency) results in skeletal maturation with increased bone mass and epiphyseal closure [26,27]. Estrogens may also play an important role in the maintenance of bone mass in adult men. A number of epidemiologic studies have shown that the slow age-related decrease in bone mass in men is more directly related to declining estrogen concentrations than to declining androgen concentrations [29–31].

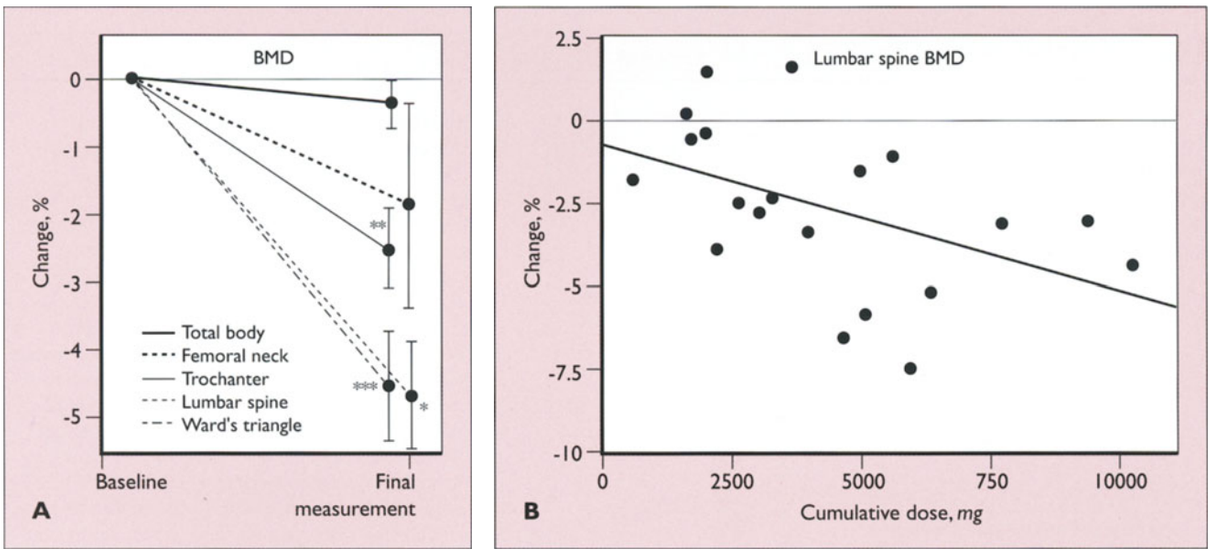



**FIGURE 10-18. A** and **B**, Glucocorticoids and bone mass in men. As in women, exposure to excessive levels of glucocorticoids has adverse effects on bone health in men. Although it is difficult to independently evaluate the skeletal actions of glucocorticoids in men (most study groups are composed of women, or men and women together), some studies have been performed specifically in men. For instance, Pearce *et al.* [32] followed otherwise normal young men who were treated for 3.7±0.6 months with high doses of corticosteroids for antisperm antibodies. Bone mineral density (BMD) declined quickly after corticosteroid therapy was begun (those who received the highest doses lost the most bone), and at the same time there were declines in markers of bone remodeling (*eg*, serum osteocalcin levels) and in serum sex steroid concentrations. These data document the importance of glucocorticoid excess in causing bone loss in men and raise the possibility that the effects of glucocorticoids are related, in part, to suppression of sex steroid levels. $*P < 0.04$; $**P < 0.01$; $***P < 0.001$ (compared to zero).

**WHICH MEN SHOULD HAVE BMD MEASURED**

Previous low trauma fracture after age 50 years
Prevalent vertebral deformity
Radiologic evidence of low bone mass
Presence of a secondary cause of osteoporosis
All men older than age 70 years?

**FIGURE 10-19.** Which men should have bone mineral density (BMD) measured? Bone mineral density measurements are not commonly obtained in men, but in several groups these measurements should be considered. It is clear that men who have suffered a low trauma fracture or who have a prevalent vertebral deformity are at considerably increased risk for subsequent fracture [9], and these men should have BMD measurements. A variety of clinical situations are known to be associated with an increased risk of fracture (see Fig. 10-11) and should raise strong consideration of BMD measurements. Some practitioners have recommended that all men older than 70 years of age should have a BMD measurement [33], although there are no data to support the cost-effectiveness of this approach.

## Diagnosis and Evaluation

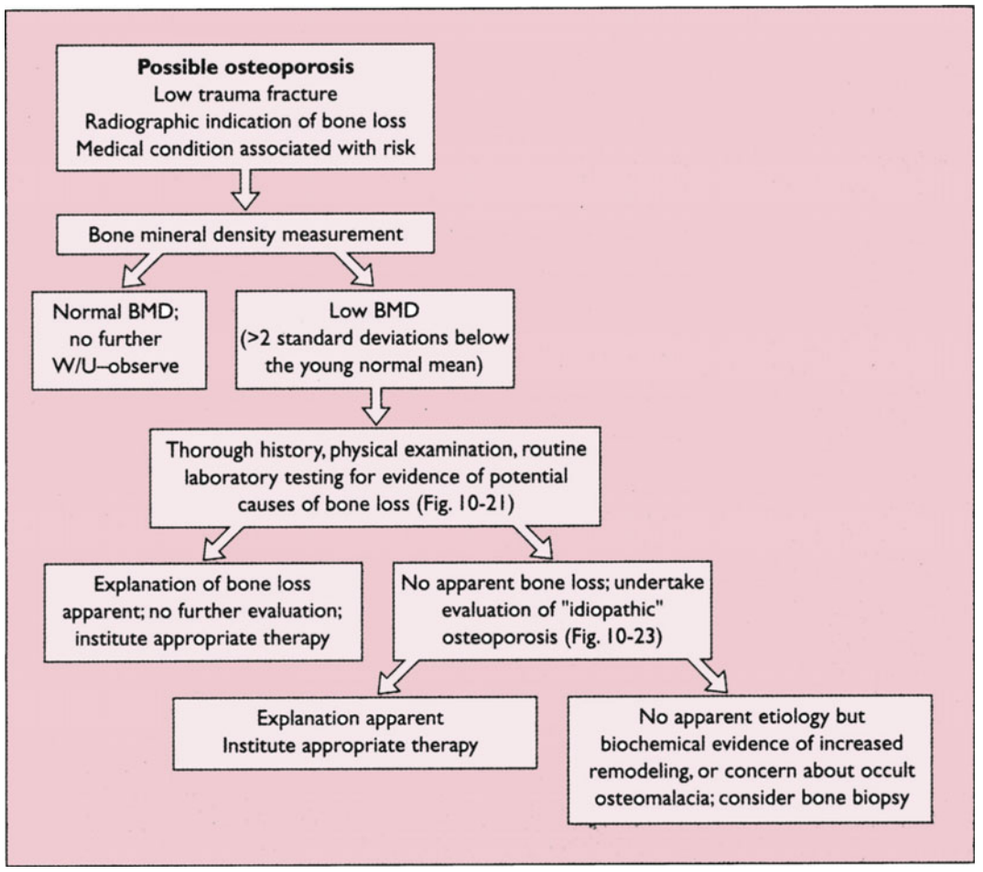



**FIGURE 10-20.** Diagnostic schema for men with suspected osteoporosis. Guidelines for the most efficient cost-effective approach for evaluating patients with low bone mass or suspected of having low bone mass are poorly validated for men and women. Recommendations therefore must be based on existing knowledge of disease epidemiology and clinical characteristics, rather than on models carefully tested in prospective studies. Within these constraints, it is possible to formulate an approach to men with osteoporosis. In some men (as in women), the diagnosis of an osteopenic metabolic bone disease can be made with basic clinical information. Most important is a clear history of low trauma fractures in the absence of evidence of a focal pathologic process (malignancy, infection, and Paget's disease). Several clinical situations exist in which the presence of osteoporosis cannot be confidently determined but should be considered probable. In these circumstances, further diagnostic steps are appropriate. These situations include the presence of suspicious fractures, radiographic presence of low bone mass, and conditions known to be associated with increased risk of bone loss. BMD—bone mineral density; W/U—work-up.

**ASSESSMENT OF THE MAN WITH LOW BONE MASS**

History
- Genetic
  - Family history
  - Ethnic background
- Nutrition
  - Calcium
  - Vitamin D intake
  - Malnutrition
- Environmental factors
  - Exercise
  - Fall frequency
  - Smoking
  - Alcohol
- Medical
  - Hypogonadism
  - Gastrointestinal disease
  - Renal disease
- Pharmacologic
  - Glucocorticoids
  - Anticonvulsants
  - Thyroid hormone
  - Heparin

Physical examination
- Height
- Spine anatomy (degree of dorsal kyphosis and lumbar lordosis)
- Hip anatomy
- Gait

Laboratory studies
- Serum creatinine, albumin, calcium, phosphorus, alkaline phosphatase, liver function tests
- Complete blood count
- Serum 25(OH) vitamin D
- Serum bioavailable testosterone
- 24-hour urine calcium, creatinine

**FIGURE 10-21.** The history, physical examination, and routine biochemical profile can be very helpful in directing a focused evaluation of a man with low bone mass. At this stage of the evaluation, emphasis is placed on determining the specific diagnosis (What is the cause of the low bone mass, osteoporosis or osteomalacia?) and identification of contributing factors in the genesis of the disorder. Risk factors for osteoporosis are explored, including family history, ethnic background, tobacco and alcohol use, lifelong dietary habits, and physical activity. A history of gastrointestinal or renal disease is elicited. Loss of height and fracture histories are also obtained. Medications that cause bone loss are identified. A history of fall frequency is obtained, and factors that increase the propensity to fall are reviewed. The systems review focuses on conditions that cause secondary osteoporosis (*eg*, endocrinopathies, immobilization, and malabsorption). The physical examination begins with an accurate measurement of height and includes a detailed examination of the spine and hip. The object of the laboratory examination is to find secondary causes of osteopenia. Routine tests, including levels of serum creatinine, albumin, calcium, phosphorus, alkaline phosphatase, and liver function tests, as well as a complete blood count, should be carried out. If, on the basis of these tests, there is evidence for medical conditions associated with bone loss (*eg*, alcoholism, hyperparathyroidism, malignancy, Cushing's syndrome, thyrotoxicosis, and malabsorption), a definitive diagnosis should be pursued with appropriate testing.

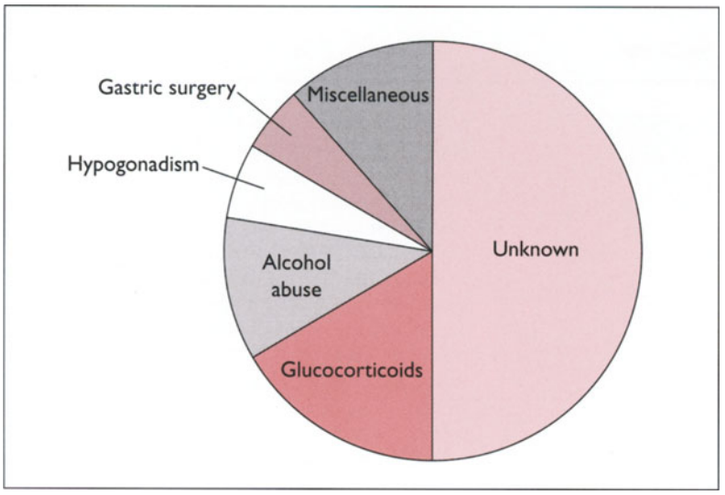



**FIGURE 10-22.** Causes of osteoporosis in men with vertebral fracture. A secondary cause of osteoporosis will be identified in approximately half of men with vertebral fracture. Of these, excessive alcohol ingestion, exogenous use of corticosteroids, and hypogonadism will account for more than half [34].

**EVALUATION OF THE MALE PATIENT WITH IDIOPATHIC OSTEOPOROSIS**

- 24-hour urine cortisol
- Serum level of thyroid-stimulating hormone
- Serum protein electrophoresis, in those >50 years to exclude multiple myeloma
- Biochemical marker of bone remodeling, to determine whether a cause of high bone turnover is present

**FIGURE 10-23.** In men with reduced bone mass in whom no clear pathophysiology is identified by the routine methods listed, it has been considered appropriate to be aggressive diagnostically, primarily because the potential for occult "secondary" causes of osteoporosis is perceived to be high. However, the incidence of occult causes of osteoporosis in men is poorly studied. The diagnostic yield and cost-effectiveness of extensive biochemical studies in men with apparently "idiopathic" osteoporosis is unknown. Nevertheless, in the absence of this information, a reasonable evaluation of men for whom the cause of osteoporosis is unknown is outlined.

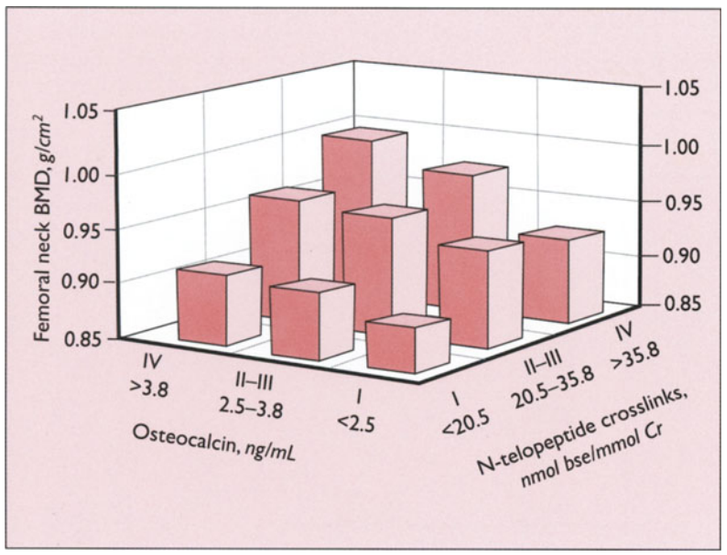



**FIGURE 10-24.** Correlation of bone remodeling markers with bone density. Aging in healthy men is associated with detectable appendicular and substantial axial bone loss. The cause of age-related bone loss in men is unknown but has been speculated to be related to an acceleration in bone turnover. Specific biochemical markers of skeletal metabolism, such as serum levels of osteocalcin and urinary excretion of N-telopeptide cross-links (NTx), correlate well with overall remodeling rates in patients with overt metabolic bone disorders and may also be of use in predicting bone mineral density (BMD) in healthy persons. In a study of 273 healthy men aged 65 to 87 years, Krall *et al.* [35] found both serum osteocalcin and urinary NTx levels to be inversely related to BMD. The difference between femoral neck BMD between persons in the low-osteocalcin low-NTx group and those in the high-osteocalcin high-NTx group was 11%. The strength of the relationship between BMD and biochemical markers of turnover is similar to previous findings in women. These observations raise the possibility that biochemical markers of bone turnover could be used as indicators of current bone status in men.

# Therapy

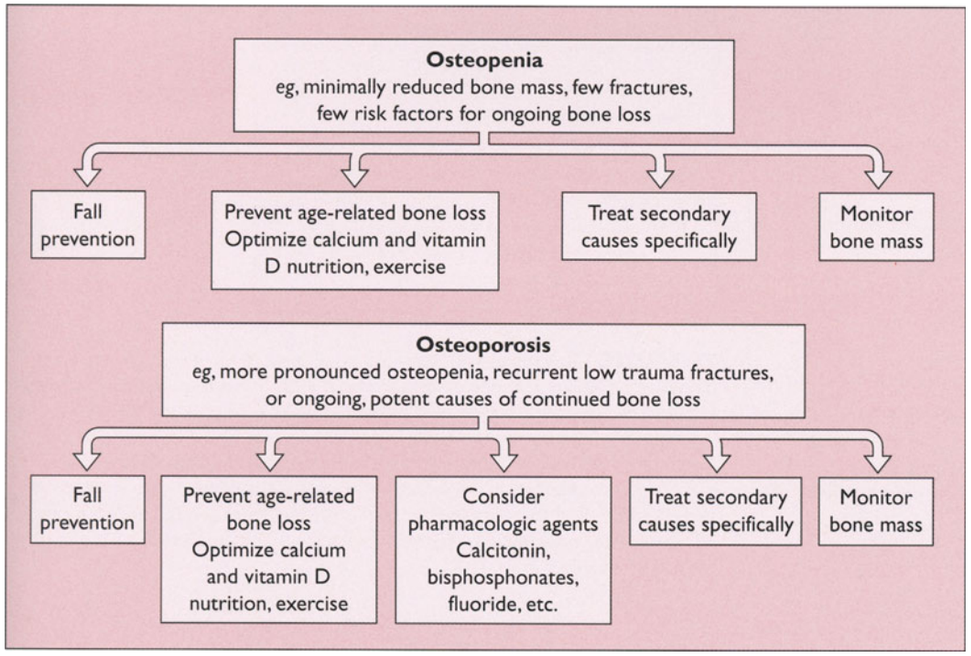
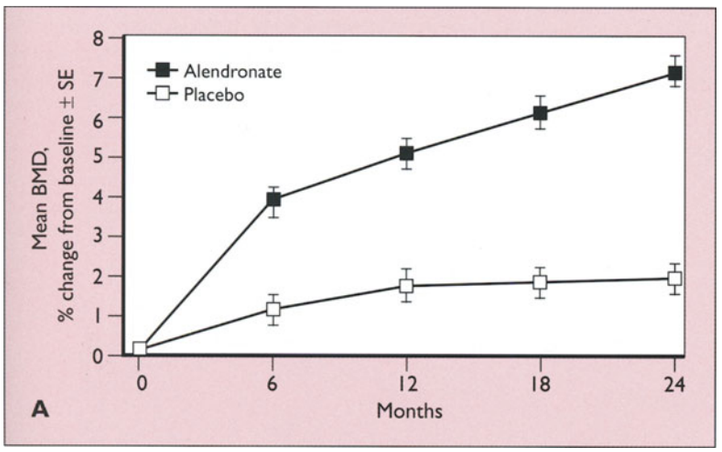



**FIGURE 10-25.** Approach to the treatment of reduced bone mass in men. In any man in whom osteoporosis has developed or is considered a clinically important possibility, efforts should be made to prevent age-related bone loss. Such efforts are the foundation on which a successful treatment plan is based and should always be a part of prevention of and therapy for osteoporosis, regardless of the other causes of bone disease that may also be present. Calcium supplements are safe and may slow bone loss. Based on suggestive but not definitive data, a recent National Institutes of Health Consensus Development Conference recommended a calcium intake of 1000 mg/d in young men and 1500 mg/d in men older than 65 years of age. Vitamin D deficiency should be suspected in all elderly persons and, if present, treated with daily vitamin D supplements. Available data strongly suggest a powerful effect of weight and mechanical force on the skeletons of men. In view of the clear decrease in physical activity and muscle strength with aging, senile bone loss in men may be related partly to a diminution of the trophic effects of mechanical force on skeletal tissues. However, a specific exercise prescription is difficult to generate with currently available information. At present, general guidelines include the use of weight-bearing exercise to the extent it can be safely undertaken and avoidance of situations that might materially increase the risk of trauma and fracture. Measures designed merely to prevent further age-related bone loss may be insufficient in men with moderate or severe osteopenia (these men are at high risk for bone loss because of coexisting and unremediable conditions) and those in whom sustained bone loss has been demonstrated. In these situations, additional pharmacologic therapies should be considered.



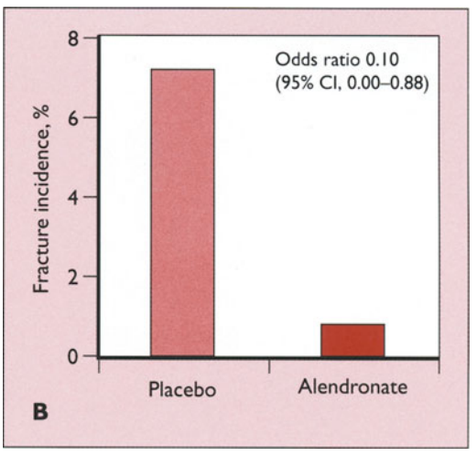




**FIGURE 10-26. A** and **B**, Treatment of osteoporosis in men with bisphosphonates. The therapy for osteoporotic disorders is not well established in men, but recently alendronate was shown to increase bone mineral density (BMD) and reduce vertebral fracture risk in men with idiopathic osteoporosis. In these studies, men with low BMD were treated with alendronate (10 mg/d) or placebo for 2 years [36]. All participants also received calcium and vitamin D supplements. In the men treated with alendronate, BMD increased in the spine, hip, and radius, and there was a reduction in the risk of vertebral fractures. Importantly, the increases in BMD with alendronate were similar in men with normal and low free testosterone levels, suggesting that alendronate treatment is useful in men with osteoporosis and hypogonadism. Therapy with weekly alendronate (70 mg/wk) has also recently been shown to be effective in increasing BMD in osteoporotic men. Thus, bisphosphonate therapy is useful in men with a variety of forms of osteoporosis (idiopathic, hypogonadal, and glucocorticoid-induced).

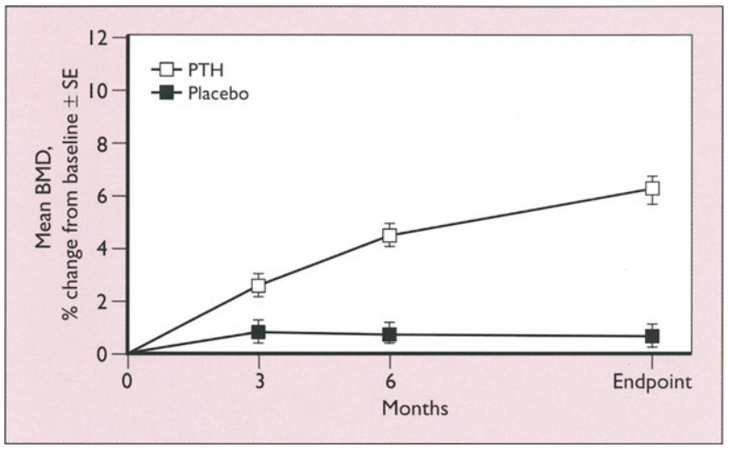



**FIGURE 10-27.** Parathyroid hormone (PTH) treatment of osteoporosis in men. In women, PTH increases bone mass and reduces the risk of vertebral and nonvertebral fractures. In men, the studies of the effectiveness of PTH are less extensive, but there appears to be a very similar response to this treatment regardless of sex. Orwoll *et al.* [37] reported that PTH treatment for an average of 11 months increased bone mineral density (BMD) at the spine and hip in men with idiopathic osteoporosis. In these studies, daily subcutaneous injections of PTH 1-34, or teriparatide (Forteo; Lilly, Indianapolis, IN), (20 μg/d) increased BMD more than did placebo injections. All men received calcium and vitamin D supplements. The 20 μg/d dose was very well tolerated, and the increase in BMD was essentially the same as that observed in women treated with PTH. PTH therapy increased BMD similarly in men who had normal or low free testosterone levels, indicating the probable usefulness of this therapy in men with osteoporosis and hypogonadism. As in women, PTH therapy is recommended for men with more severe osteoporosis (very low BMD or osteoporosis with previous fractures).

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# 11

# Osteoporosis Associated with Systemic Illness and Medications

*Paul D. Miller*

Osteoporosis is defined as low bone mass, microarchitectural bone deterioration, and susceptibility to fracture. The primary causes of osteoporosis are estrogen deficiency after menopause and advanced age. Ten secondary causes of osteoporosis have been categorized by organ system or systemic disease. Each of these secondary causes is associated with a negative calcium balance or defects in bone formation or resorption at the bone remodeling unit. This chapter focuses on the diagnostic characteristics of these secondary causes.

Osteoporosis may be related to gastrointestinal disorders. In most of these disorders, the bone loss is associated with a rapid gastrointestinal transit time that precludes adequate calcium absorption. Osteoporosis may also be related to chronic liver, kidney, or pancreatic diseases. Chronic liver disease may impair the conversion of cholecalciferol to 25-hydroxycholecalciferol, reduce the production of insulin-like growth factor-I, and cause iron overload in tissues; all of these may be related to bone loss. Renal failure is associated with changes in calcium metabolism, hypogonadism, hyperparathyroidism, inadequate production of 1,25-dihydroxyvitamin D, and chronic metabolic acidosis; these conditions, in turn, can cause osteoporosis. Several types of medications have also been associated with osteoporosis. The mechanism of bone loss stems from the type and action of the medication. Low bone mass and fractures may also be related to disorders of bone marrow. Bone resorption and osteoporosis may be associated with immobilization or microgravity environments. Immobilization (affecting the total body, occurring after an accident causing quadriplegia, or required for a single limb) can induce excessive bone resorption and osteoporosis. The same excessive bone resorption is seen in people living in microgravity environments. The accelerated bone resorption seen in these circumstances is associated with increased urinary calcium excretion.

Osteoporosis has also been shown to be related to endocrine disorders. The mechanisms of these disorders are related to endocrine gland malfunction. Osteoporosis has been associated with several genetic disorders of metabolism, including Marfan syndrome, homocystinuria, Ehlers-Danlos syndrome, and hypophosphatasia. These genetic disorders of metabolism may be associated with low bone mass or bone loss. Disorders of connective tissue metabolism may be accompanied by inadequate bone mineralization as well, because the substrate for calcification is defective. Osteoporosis is also often associated with nutritional disorders related to calcium and vitamin D. Finally, osteoporosis may be related to osteomalacia and osteogenesis imperfecta.

This chapter is designed to help physicians understand the characteristics and mechanisms of secondary causes of osteoporosis and to assist with the diagnosis of the many causes of bone loss. It stresses the importance of carefully evaluating each patient with low bone mass before administering therapeutic interventions.

**TEN SECONDARY CAUSES OF OSTEOPOROSIS**

- Gastrointestinal diseases
- Liver, kidney, or pancreatic diseases
- Medications
- Bone marrow disorders
- Immobilization and microgravity
- Endocrine disorders
- Pregnancy
- Genetic metabolic disorders
- States of nutritional deficiency
- Osteomalacia and osteogenesis imperfecta

**FIGURE 11-1.** Ten categories of disorders associated with secondary causes of osteoporosis listed according to the organ system involved or the system disease associated with bone loss.

# Osteoporosis Related to Gastrointestinal Diseases

**GASTROINTESTINAL DISEASES AND CONDITIONS ASSOCIATED WITH OSTEOPOROSIS**

- Hemigastrectomy or total gastrectomy
- Intestinal bypass
- Asymptomatic celiac disease
- Small intestinal malabsorption conditions (eg, Whipple's disease, scleroderma)
- Inflammatory bowel disease

**FIGURE 11-2.** Some gastrointestinal diseases and conditions associated with osteoporosis [1]. Patients with hemigastrectomy or total gastrectomy may develop osteoporosis or, less frequently, osteomalacia. The osteoporosis is related to a rapid gastrointestinal transit time, which precludes adequate nutrient (eg, calcium) absorption. Osteomalacia, which may develop in selected patients, is due to a lack of bile-salt binding to fat-soluble vitamin D. This causes inadequate vitamin D absorption in the terminal ileum. Surgical intestinal bypass may also cause osteoporosis or osteomalacia by the same pathophysiologic mechanisms. Quantitative bone histology suggests that bone formation is impaired in gastrectomized animal models. Patients with Crohn's disease and asymptomatic nontropical sprue (celiac disease) often have low bone mass.

**DIAGNOSTIC CLUES FOR DETECTION OF ASYMPTOMATIC CELIAC DISEASE**

- Low bone mass
- Normal serum 25-hydroxyvitamin D concentrations
- Normal serum bone-specific alkaline phosphatase activity
- 24-hour urine calcium excretion < 50 mg/d
- Elevated levels of serum antigliadin or antiendomysial antibodies (levels may also be normal)
- Iron deficiency
- Definitive diagnosis on small-bowel biopsy

**FIGURE 11-3.** Diagnostic clues for the detection of asymptomatic celiac disease. Asymptomatic celiac disease (nontropical sprue) is an underdiagnosed bowel condition leading to osteoporosis, not osteomalacia [2]. One of the most important clues is a 24-hour urine calcium excretion less than 50 mg/d. This low value suggests calcium malabsorption or extremely low calcium intake. Low urinary calcium excretion is valid for the determination of calcium malabsorption if the serum calcium level is within the normal range and the glomerular filtration rate exceeds 50 mL/min (determined by creatinine clearance). If hypocalcemia or significant renal failure is present, low urinary calcium excretion may be due to these disorders, rather than to calcium malabsorption. High serum antigliadin and antiendomysial antibodies are also associated with celiac disease. However, these antibodies may be undetectable in some patients with this condition. Thus, the absence of these antibodies does not necessarily exclude a diagnosis of celiac disease. Patients with celiac disease often have normal serum 25-hydroxyvitamin D levels because the disease begins in the proximal small intestine and vitamin D is absorbed in the terminal ileum. Celiac disease causes selective malabsorption of calcium and iron. Therefore, unexplained iron deficiency may also be a clue to the presence of this disease. If a hypocalciuric patient has unexplained low bone mass, bone loss, or fractures, a small intestinal biopsy is the definitive method for diagnosing celiac disease. Treatment with a gluten-free diet can increase bone mass.

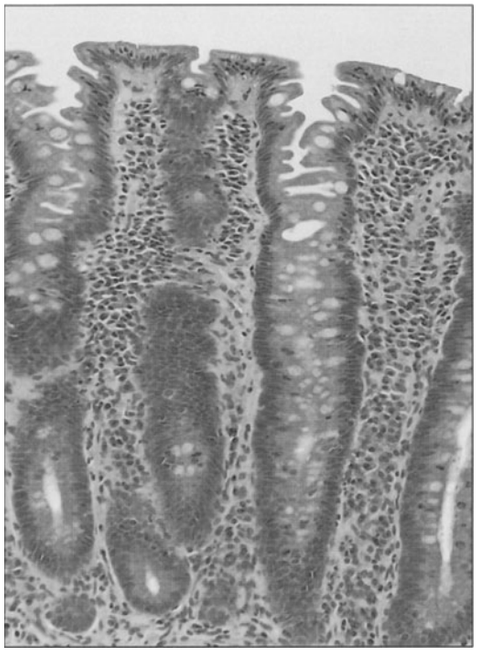

**FIGURE 11-4.** Small bowel biopsy specimen from a patient with celiac disease. This condition is diagnosed by histologic features demonstrating the loss of villous architecture and infiltration of the lamina propria with abundant mononuclear cells.

## Osteoporosis Related to Liver, Kidney, or Pancreatic Diseases

**CHRONIC LIVER, KIDNEY, AND PANCREATIC DISEASE RELATED TO OSTEOPOROSIS**

- Chronic liver disease
- Hemochromatosis or iron accumulation over osteoid surfaces
- Chronic renal failure
- Chronic renal tubular acidosis
- Hypercalciuria
- Renal phosphate wastage
- Chronic pancreatic insufficiency

**FIGURE 11-5.** Some chronic liver, kidney, or pancreatic diseases associated with osteoporosis. Chronic liver disease may lead to osteoporosis or osteomalacia [3]. Conversion of cholecalciferol to 25-hydroxycholecalciferol, which normally occurs in the liver, may be impaired by chronic liver disease. This impairment may lead to osteoporosis or osteomalacia. The liver is the primary source of circulating insulin-like growth factor-1 (IGF-1), and some cases of osteoporosis related to liver disease may be due to the inadequate production of this stimulator of bone formation. In this regard, the elevated IGF-1 concentrations observed in patients with chronic hepatitis C may be responsible for the elevated bone mass observed in these patients. The osteoporosis observed in patients with chronic renal failure may be caused by any of the following: hypogonadism, long-term heparin exposure, secondary hyperparathyroidism, inadequate renal production of 1,25-dihydroxyvitamin D, or chronic metabolic acidosis [4]. Chronic metabolic acidosis, as seen in patients with renal tubular acidosis, may lead to osteoporosis when bone releases calcium to buffer the serum acid load. This process is often associated with hypercalciuria and may also lead to osteomalacia if other renal tubular defects (such as renal phosphate wastage or inadequate proximal tubular production of 1,25-dihydroxyvitamin D) are present.

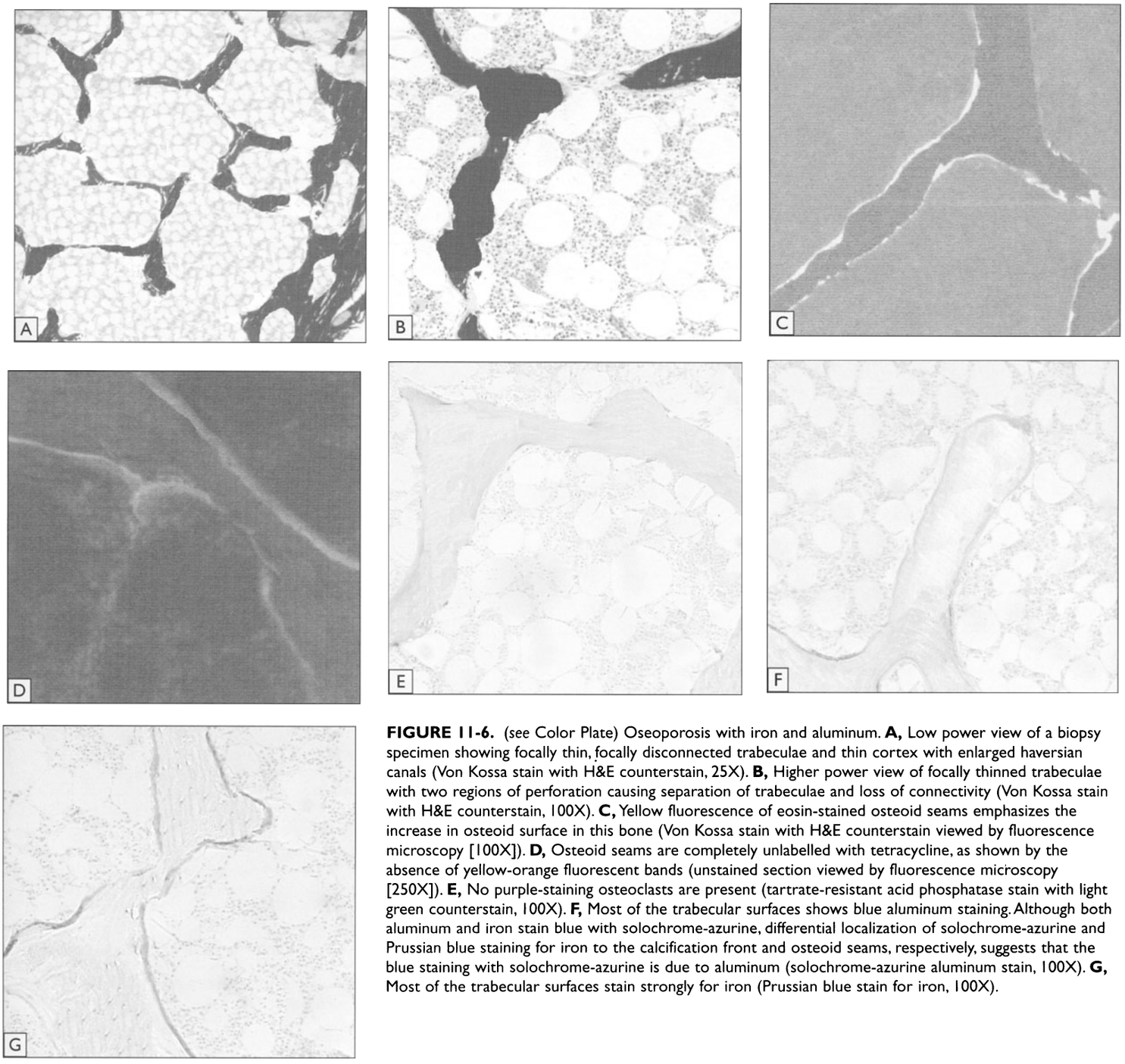


**FIGURE 11-6.** (see Color Plate) Oseoporosis with iron and aluminum. **A,** Low power view of a biopsy specimen showing focally thin, focally disconnected trabeculae and thin cortex with enlarged haversian canals (Von Kossa stain with H&E counterstain, 25X). **B,** Higher power view of focally thinned trabeculae with two regions of perforation causing separation of trabeculae and loss of connectivity (Von Kossa stain with H&E counterstain, 100X). **C,** Yellow fluorescence of eosin-stained osteoid seams emphasizes the increase in osteoid surface in this bone (Von Kossa stain with H&E counterstain viewed by fluorescence microscopy [100X]). **D,** Osteoid seams are completely unlabelled with tetracycline, as shown by the absence of yellow-orange fluorescent bands (unstained section viewed by fluorescence microscopy [250X]). **E,** No purple-staining osteoclasts are present (tartrate-resistant acid phosphatase stain with light green counterstain, 100X). **F,** Most of the trabecular surfaces shows blue aluminum staining. Although both aluminum and iron stain blue with solochrome-azurine, differential localization of solochrome-azurine and Prussian blue staining for iron to the calcification front and osteoid seams, respectively, suggests that the blue staining with solochrome-azurine is due to aluminum (solochrome-azurine aluminum stain, 100X). **G,** Most of the trabecular surfaces stain strongly for iron (Prussian blue stain for iron, 100X).

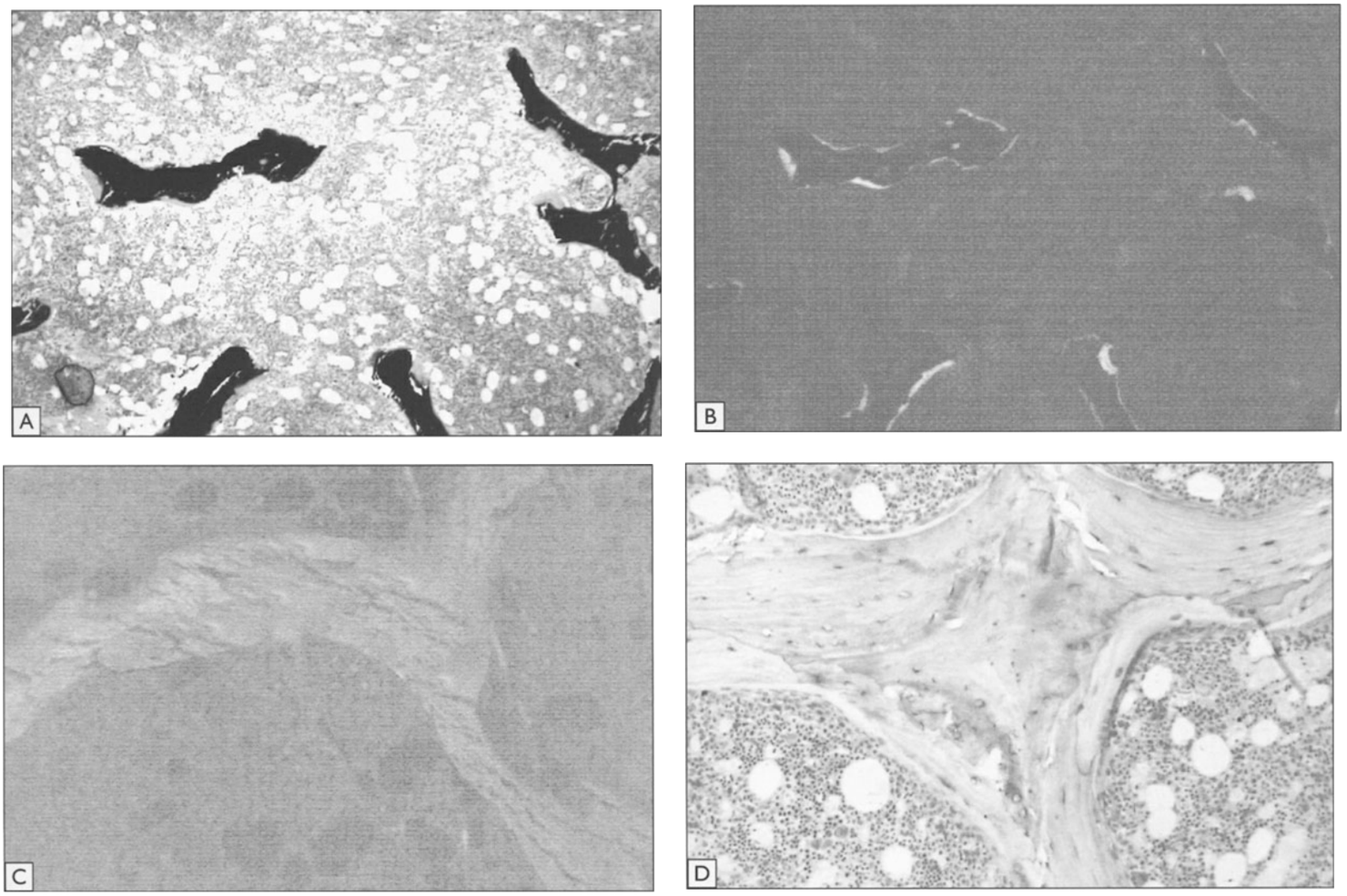


**FIGURE 11-7.** (see Color Plate) Aplastic bone disease. **A,** Short, widely separated osteoid seams are disconnected, and focal prominent osteoid seams are seen. **B** shows the same field viewed with fluorescent light to better illustrate the osteoid seams. The prominent osteoid seams suggest that there may be a mineralization defect (Von Kossa stain with H&E counterstain, 50X). **C,** Absence of fluorescent tetracycline bands indicates that there is no mineralization, but this could also be due to lack of bone formation (unstained section viewed by fluorescence microscopy [100X]). **D,** The absence of purple-staining osteoclasts in the section indicates that bone resorption is decreased. The azure stain shows prominent basophilic cement lines, indicative of past active remodeling; however, a lack of osteoblasts, which should stain prominently with azure B, suggests that there is no current increased bone formation. Decreased tetracycline therefore may due to a defect in bone formation (section stained for tartrate-resistant acid phosphatase with an azure B counterstains, 100X).

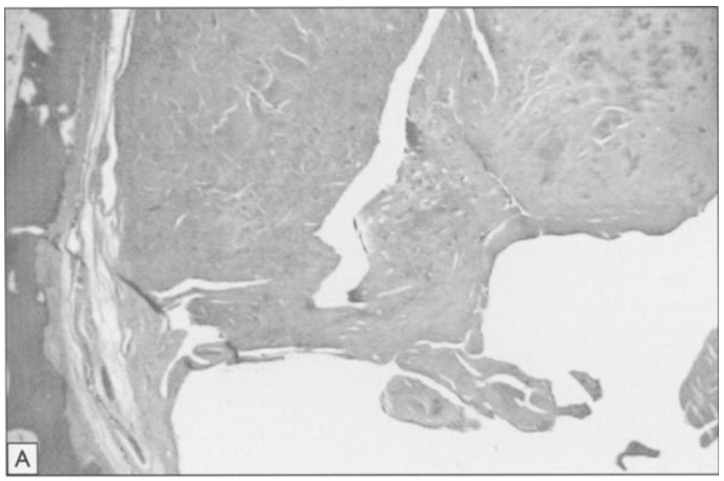


**FIGURE 11-8.** Amyloidosis. **A,** Hematoxylin and eosin–stained, decalcified section, 25X.

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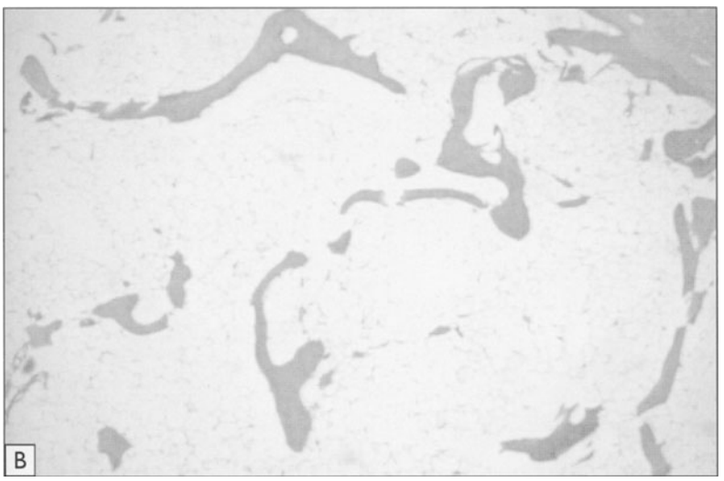


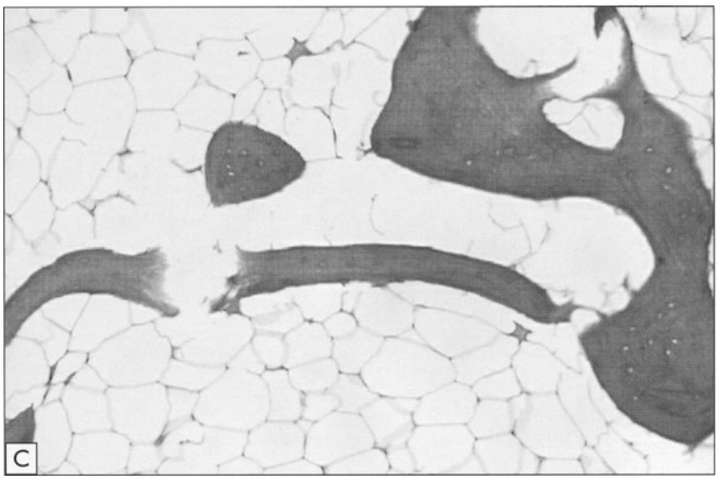
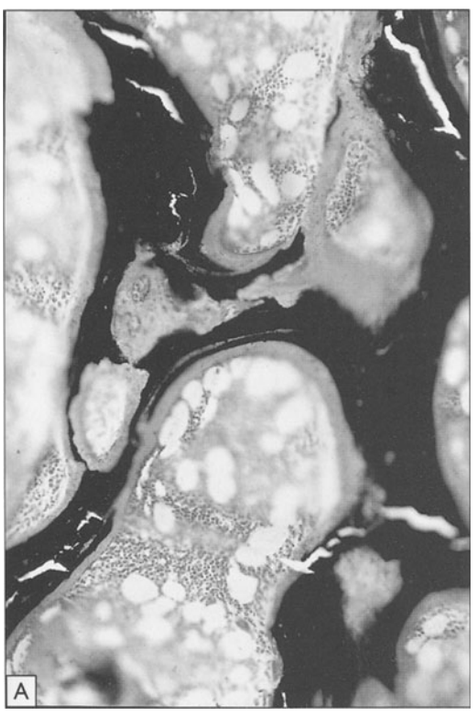




**FIGURE 11-8.** *(Continued)* **B** and **C,** Osteopenic trabecular bone consists of thin, nonanastomosing, widely separated trabeculae surrounded by a thin cortex. At high magnification, the bone surfaces are smooth without osteoblasts or osteoclasts, and the marrow is composed entirely of adipose tissue. There is no evidence of high turnover or osteomalacic bone disease (hematoxylin and eosin–stained sections of decalcified cortical and trabecular bone, **B,** 25X; **C,** 100X).



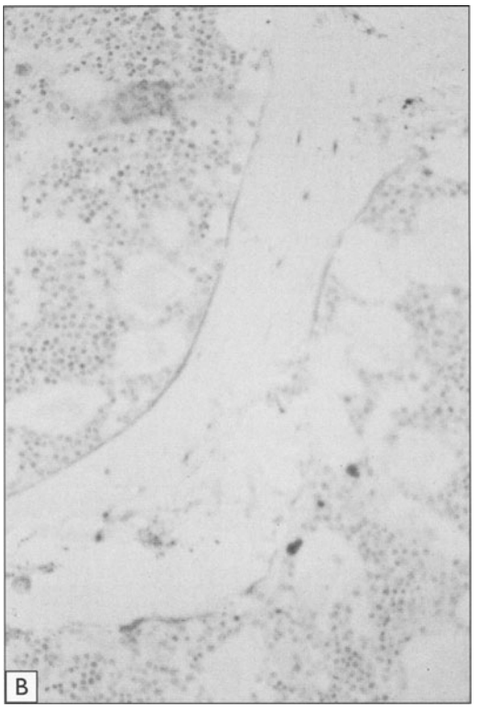




**FIGURE 11-9.** (see Color Plate) **A**, Bone biopsy specimen from a patient with iron overload and osteomalacia (hemochromatosis). Abundant thick osteoid seams (shown in pink) are the characteristic finding of osteomalacia. **B**, Bone biopsy specimen from a patient with iron overload and osteoporosis. The liver is also responsible for the proper disposal of iron, and iron overload may lead to iron accumulation in other tissues, including bone. Iron deposited in bone (shown in blue) may accumulate on osteoid surfaces and lead to frank osteomalacia or osteoporosis. Although classic hemochromatosis is usually associated with elevated serum iron indices, iron may accumulate in bone in the absence of elevated serum ferritin levels. In cases of unexplained osteoporosis or fracture, iron accumulation can be diagnosed only by bone biopsy.

**CAUSES OF HYPERCALCIURIA**

- Idiopathic hypercalciuria
- Primary hyperparathyroidism
- Absorptive hypercalciuria
- Chronic metabolic acidosis
- Hypercalcemia
- Vitamin D excess
- Vitamin A excess
- Sarcoidosis and other granulomatous diseases
- Immobilization and microgravity
- Glucocorticoid excess (including Cushing disease)

**FIGURE 11-10.** Some causes of hypercalciuria. Osteoporosis may be related to hypercalciuria. Hypercalciuria (calcium excretion >250 mg/d in women and >300 mg/d in men) may be due to any of the causes shown in this figure. Osteoporosis may be related to idiopathic hypercalciuria (renal), and normalization of hypercalciuria with thiazides may be associated with increases in bone mass. However, this increase in bone mass may also be due to a direct effect of thiazides on bone. Thiazides may also be used therapeutically to normalize urinary calcium excretion in patients with glucocorticoid-induced hypercalciuria.

# Osteoporosis Related to Medication Administration

**MEDICATIONS ASSOCIATED WITH OSTEOPOROSIS**

- Short- or long-term glucocorticoid administration
- Long-term administration of gonadotropin-releasing hormone agonist
- Long-term therapy with antiseizure medication
- Long-term heparin treatment
- Long-term tetracycline administration
- Possible associations: Depo-Provera, cyclosporine, methotrexate, lithium, antidepressant agents, antipsychotic drugs

**FIGURE 11-11.** Some medications associated with osteoporosis [5]. Glucocorticoids induce bone loss through many mechanisms [6]. The rate of bone loss is dose dependent. Bone loss occurs even with low dosages (<7.5 mg of prednisone per day or its dose equivalent), suggesting that the effects of glucocorticoids on bone may be cumulative. Use of inhaled steroids over the long term has also been associated with bone loss. Long-term therapy with gonadotropin-releasing hormone (GnRH) agonist, for patients with disorders such as premenstrual syndrome (PMS) or prostate cancer, induces bone loss. Intermittent therapy with GnRH for infertility may induce temporary bone loss that is reversed after discontinuation of therapy. Long-term antiseizure therapy may induce bone loss through several mechanisms. Long-term phenytoin sodium or phenobarbital use has been associated with osteomalacia, particularly in institutionalized children with vitamin D deficiency. However, these compounds may cause defects in hepatic activation of 25-hydroxyvitamin D, which is associated with mineralization defects. Adult patients treated with antiseizure medications generally have high-turnover osteoporosis, rather than osteomalacia. Recent data in animals suggest that these medications may directly affect bone turnover, leading to impaired bone formation as well. Long-term heparin or tetracycline administration may induce bone loss and fractures. The bone loss and increased risk of fracture is dose and duration dependent, and the mechanism of increased bone resorption is unclear. Depo-Provera has been associated with low bone mass in premenopausal women using it for birth control. The bone loss may not be fully reversed after discontinuation of therapy with the drug. This progestational agent suppresses pituitary secretion of follicle-stimulating hormone and luteinizing hormone sufficiently to result in low concentrations of estradiol, which may explain the bone loss. Prospective studies are under way to determine whether this bone loss is significant. In animal models, administration of cyclosporine or methotrexate has been associated with bone loss. Human studies suggest that this bone loss may not be clinically relevant. Lithium administration may cause hyperparathyroidism and hypercalcemia, which may affect bone. However, this has not been adequately investigated. Certain antidepressant and antipsychotic medications have been associated with elevated prolactin levels and low bone mass in small cross-sectional studies. Elevated prolactin levels may lead to bone resorption; thus, these medications merit further investigation.

# Osteoporosis Related to Bone Marrow Disorders

**BONE MARROW DISORDERS ASSOCIATED WITH OSTEOPOROSIS**

- Multiple myeloma
- Mastocytosis
- Thalassemia
- Gaucher disease
- Beta$_2$-macroglobulinemia
- Lymphoma

**FIGURE 11-12.** Some bone marrow disorders potentially associated with osteoporosis. Thalassemia may be associated with osteoporosis and mineralization defects as well. Gaucher disease and its accompanying bone marrow expansion, has been associated with osteoporosis and hip fracture. Beta$_2$-macroglobulinemia or amyloid accumulation in bone, sometimes observed in chronic renal failure or amyloidosis, may also be associated with osteoporosis.

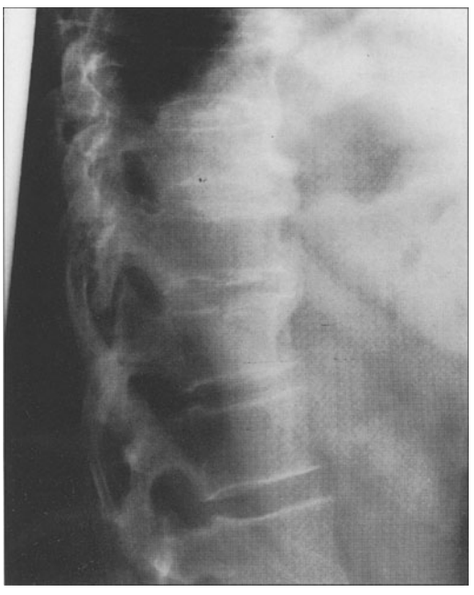


**FIGURE 11-13.** Radiograph of new vertebral compression fracture in a 50-year-old man with multiple myeloma without anemia or elevated erythrocyte sedimentation rate. Multiple myeloma is a common cause of osteoporosis and often presents with vertebral compression fractures [7]. Immunoelectrophoresis should be performed in patients 50 years of age or older who have vertebral fractures.

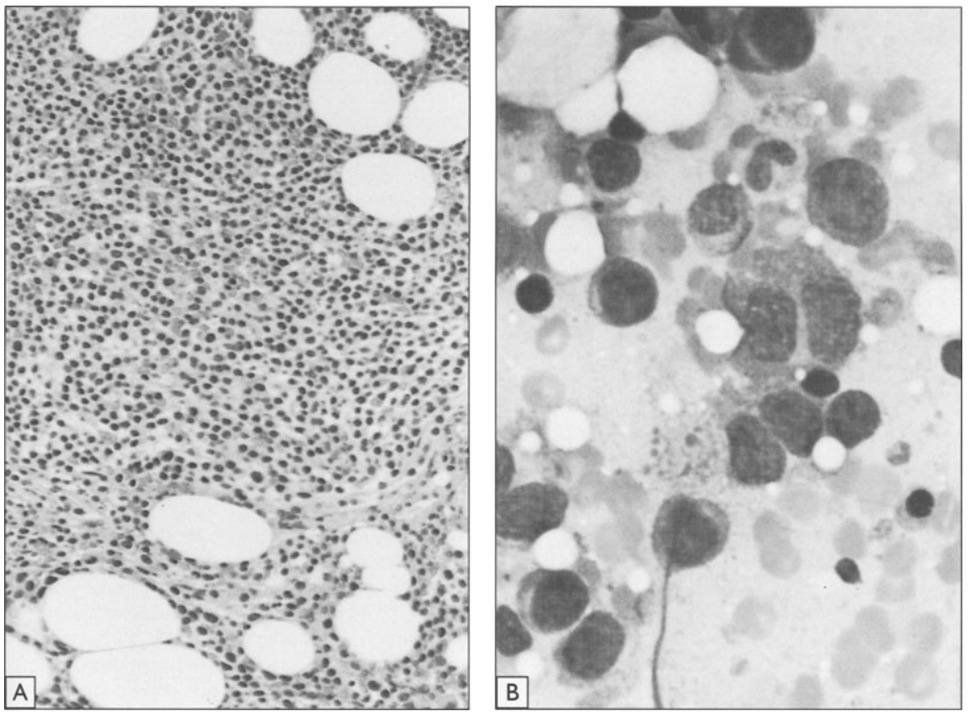



**FIGURE 11-14.** Bone marrow biopsy specimens from patient shown in Figure 11-13. A monoclonal protein spike should be followed by a bone marrow examination, which will definitively diagnose myeloma. **A**, Diffuse replacement of bone marrow with plasma cells. **B**, Higher magnification shows cells with characteristic halos surrounding the plasma nuclei.

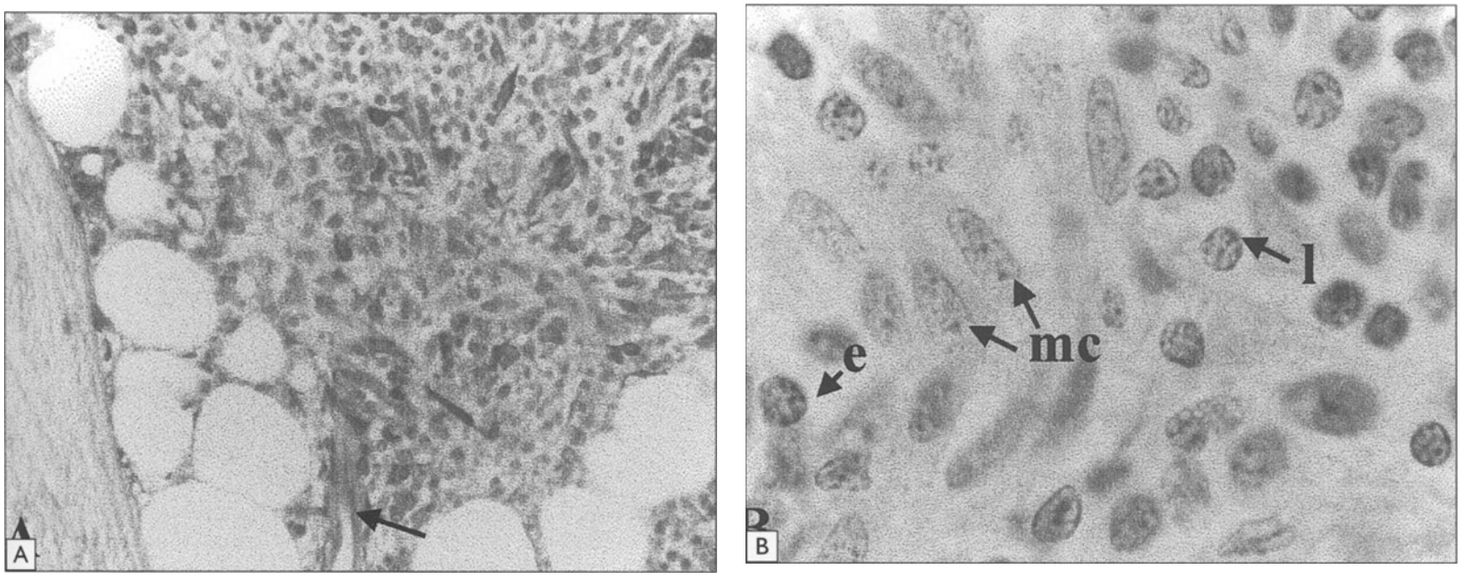



**FIGURE 11-15.** (*see* Color Plate) Histologic findings of bone marrow from a patient with mastocytosis. Mastocytosis is an unusual cause of osteoporosis [8]. Patients with mastocytosis may have skin manifestations (hives or other nonspecific rashes) and gastrointestinal symptoms. Unexplained severe low bone mass, bone loss, fractures, or high biochemical markers of bone resorption may be due to mastocytosis. Histologic characteristics of bone marrow may often be diagnostic of mastocytosis.

**A**, Glycol methacrylate–embedded iliac crest biopsy specimen. A typical mast cell aggregate adjacent to bone is penetrated at one end by a small arteriole (*arrow*). The aggregate consists of large, purple, elongated spindle-shaped mast cells admixed with small, round lymphocytes. (Stain, azure A at a pH of 4.5; original magnification, ×200.) **B**, Section adjacent to that shown in **A**. The large mast cells (mc) show only weak cytoplasmic staining and are admixed with smaller eosinophils (e) and lymphocytes (l). (Stain, hematoxylin and eosin; original magnification, ×1000.)

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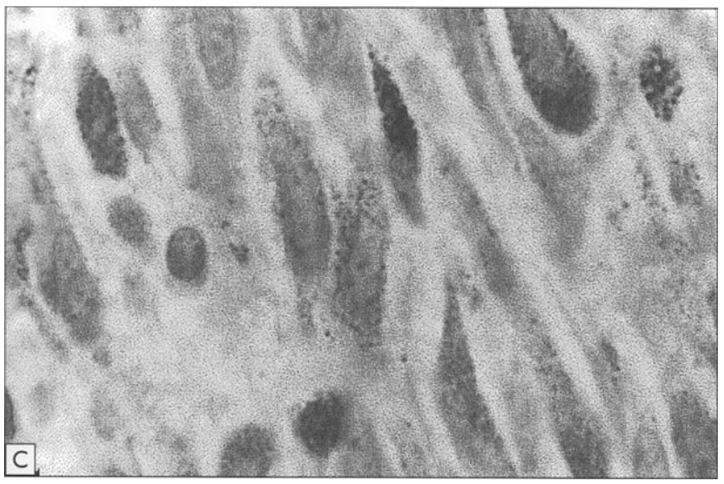


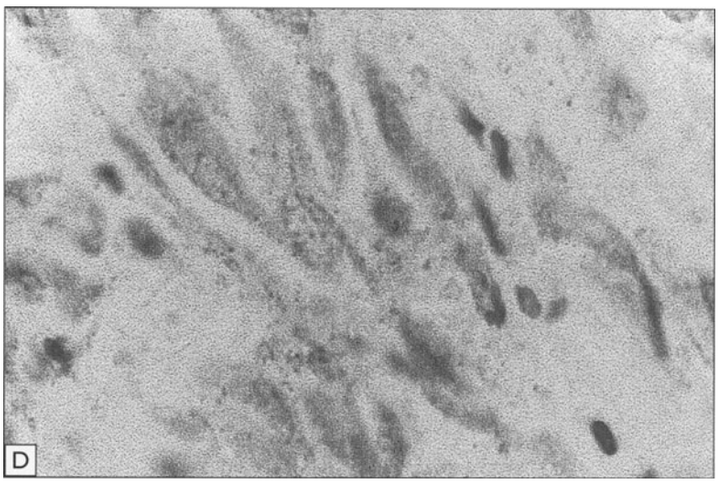




**FIGURE 11-15.** (*Continued*) **C**, Higher-power view of the section shown in **A**. Purple staining of mast cells is the result of strong staining of granules with azure. The normal blue absorption peak of azure undergoes a red metachromatic shift induced by the high negative charge density of heparin in the granules. (Original magnification, ×1000.) **D**, Section adjacent to those in **A** and **B**. The mast cell granules also stain positively for this enzyme. (Stained for tartrate-resistant acid phosphatase; original magnification, ×1000.)

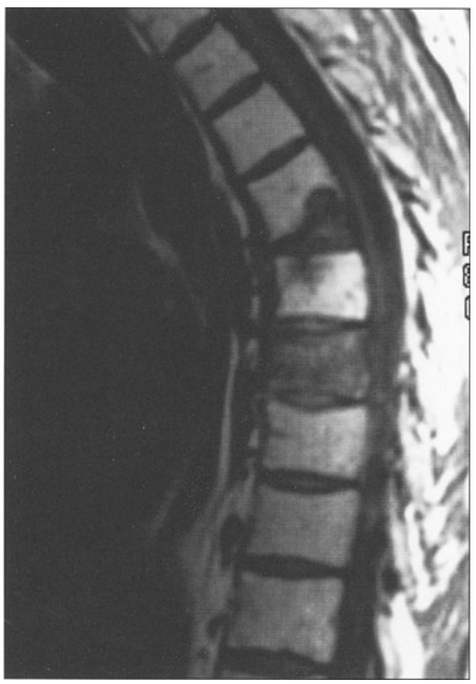


**FIGURE 11-16.** Magnetic resonance imaging scan of a man with an acute vertebral compression fracture. Lymphoma infiltration in the bone marrow may lead to localized osteoporosis and fracture in the involved bone [9]. The lymphoma infiltration is depicted by the "ivory" vertebra. Vertebral biopsy confirmed the diagnosis of lymphoma.

## Osteoporosis Related to Endocrine Disorders

**ENDOCRINE DISORDERS ASSOCIATED WITH OSTEOPOROSIS**

| | |
|---|---|
| Hyperparathyroidism | Hypogonadism (female and male) |
| Cushing syndrome | Male aromatase deficiency |
| Hyperthyroidism | Hypothalamic-pituitary dysfunction |
| Hyperprolactinemia | Acromegaly |

**FIGURE 11-17.** Some endocrine disorders associated with osteoporosis.

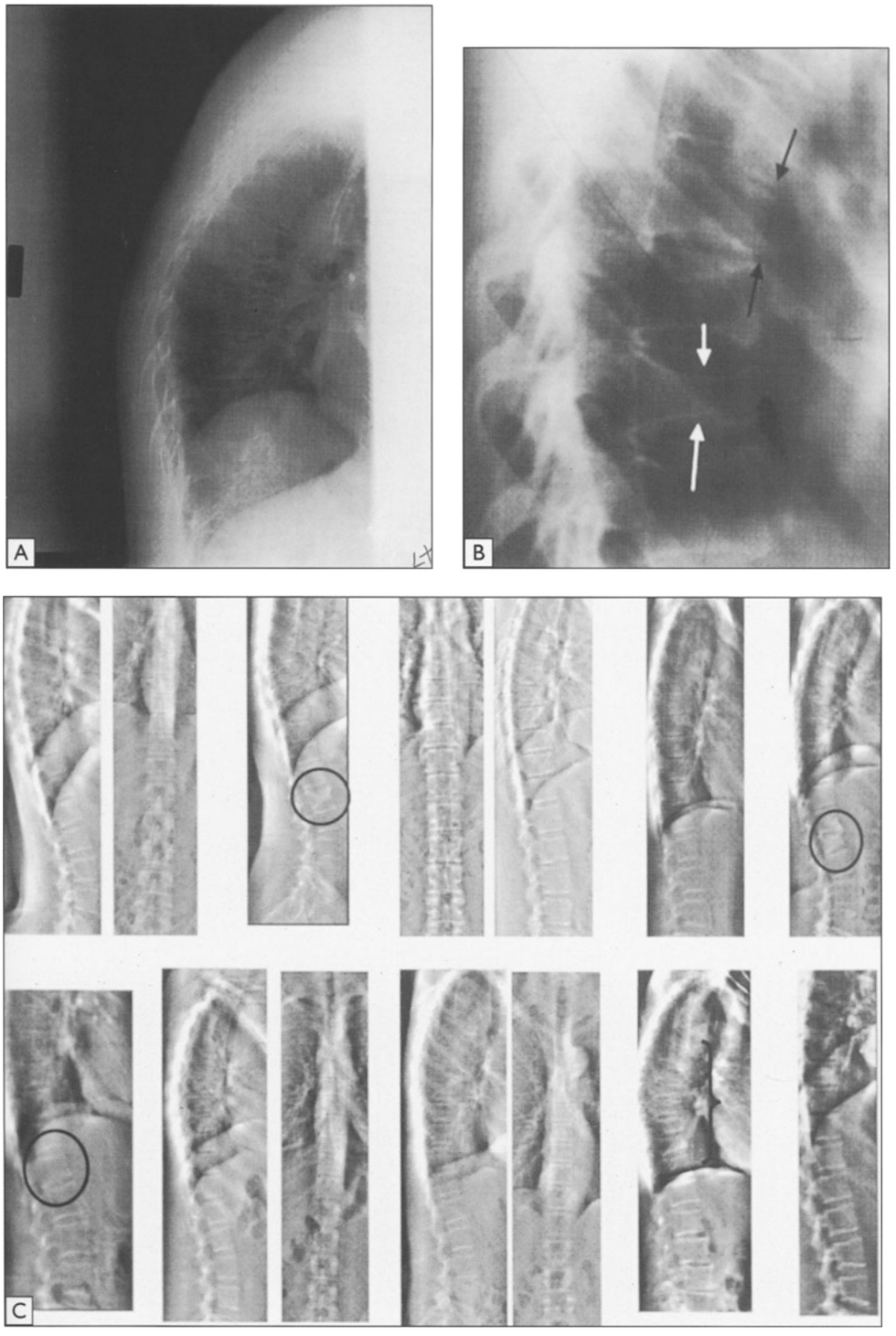



**FIGURE 11-18. A,** Radiograph of vertebral compression fractures in a woman with postmenopausal osteoporosis. Most vertebral compression fractures are asymptomatic and are underdetected. This woman, who had multiple vertebral compression fractures, experienced no back pain. The prevalence of vertebral fractures approaches 20% in white women at age 70 years. **B,** Osteoporosis can be diagnosed, based on the presence or history of an osteoporotic fracture; however, a fracture is not required for diagnosis. The loss of height should trigger an assessment for the possible presence of vertebral fracture. This can be done as a routine radiograph or by bone densitometry technology, instant vertebral assessment (**C**), or lateral vertebral assessment.

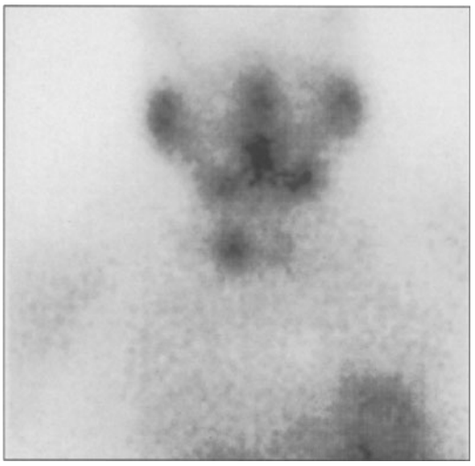
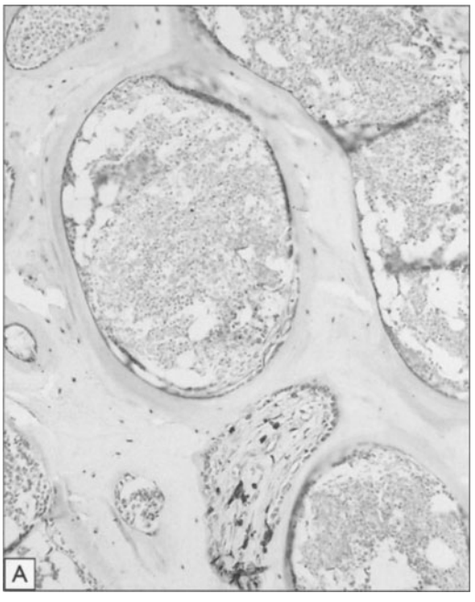
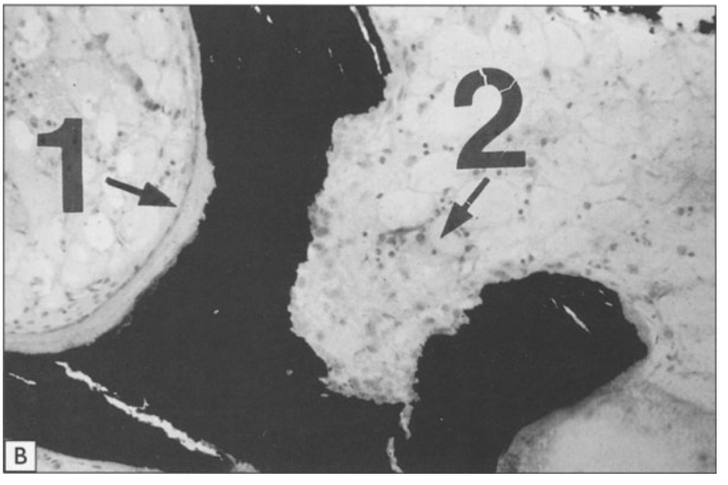


**FIGURE 11-19.** Sestamibi scan showing an enlarged parathyroid gland. Primary hyperparathyroidism may lead to excessive bone resorption and osteoporosis [10]. The cortical bone sites seem to be affected more frequently than the cancellous bone sites, although the latter bone structure may not be spared in subsets of patients. Even if cancellous bone mass is not declining, parathyroidectomy is often followed by increases in bone mass. In some cases, elevated parathyroid hormone and serum calcium levels are sufficient to establish the diagnosis. However, the documentation of enlarged parathyroid glands using newer radioisotope scans (sestamibi) is reassuring and helps guide the parathyroid surgeon.



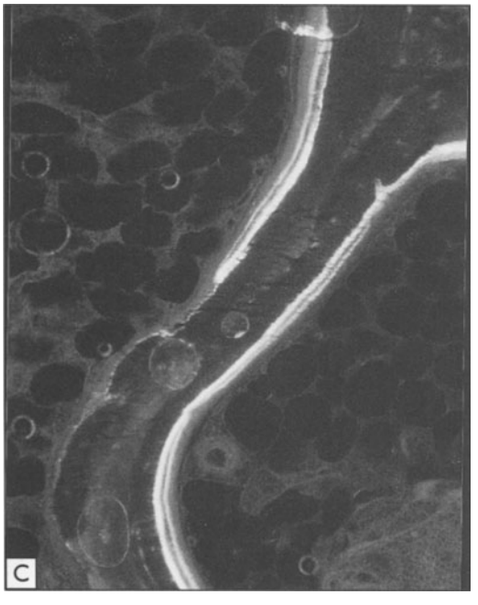




**FIGURE 11-20.** (see Color Plate) Quantitative bone histomorphometry. Increased tetracycline labeling, increased mineralization rates, and increased osteoclast numbers may be useful in cases of hyperparathyroidism, which are difficult to diagnose. **A**, Abundant osteoclast cells in purple. **B**, Two histologic features of hyperparathyroidism: (1) abundant osteoblasts creating bone matrix (pink seam) and (2) osteoclasts inducing bone resorption (scalloped borders). (**C**) Increased mineralization (broad tetracycline bands) related to excess parathyroid activity.

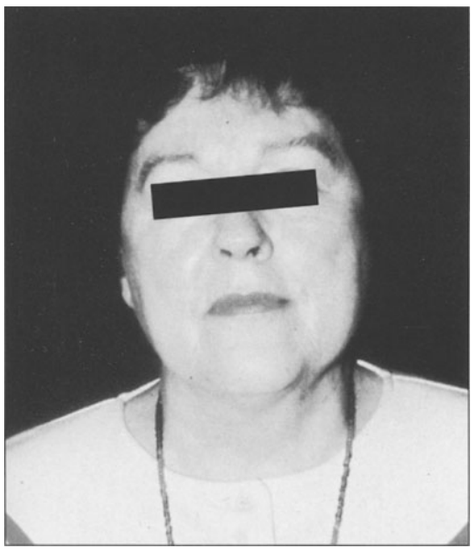


**FIGURE 11-21.** Facial characteristics of a patient with Cushing disease.

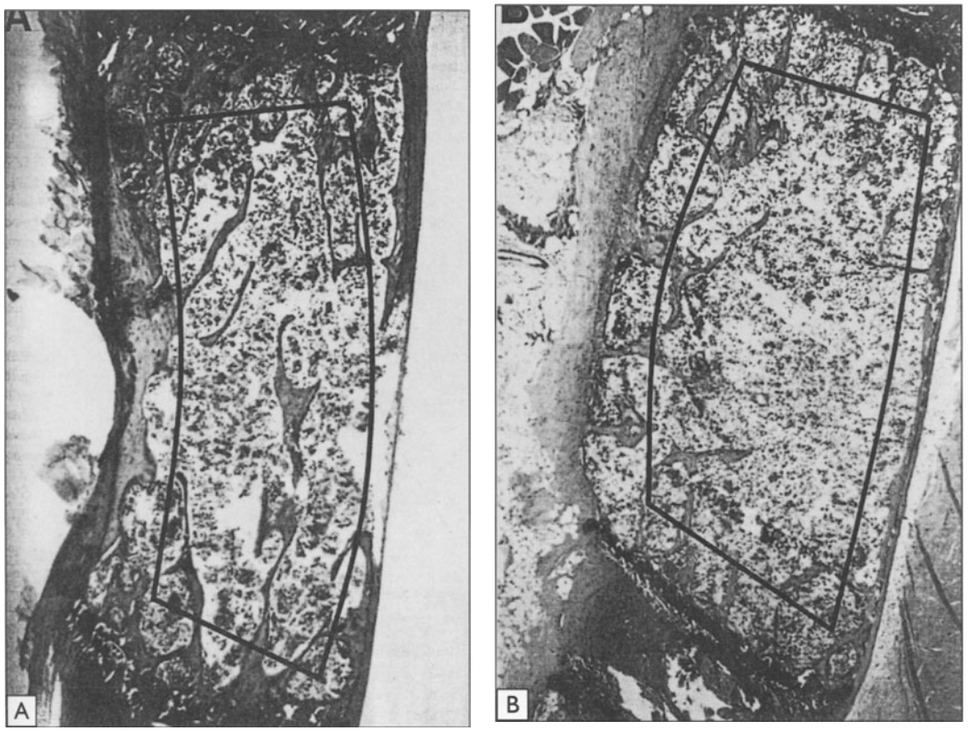



**FIGURE 11-22.** Photomicrographs of the effects of placebo (**A**) and prednisolone (**B**) on murine vertebral cancellous bone. Cushing syndrome is characterized by excess glucocorticoid production from an adrenal tumor, adrenal hyperplasia due to pituitary adrenocorticotropic (ACTH) excess, or ectopic ACTH excess, all of which lead to increased bone resorption and osteoporosis [11]. Bone histologic characteristics in patients with glucocorticoid excess are distinct from those in patients with osteoporosis due to estrogen deficiency. Trabecular connectivity is preserved in patients with glucocorticoid excess, and trabecular bone is often perforated in patients with osteoporosis due to estrogen deficiency. Bone histology in chronic glucocorticoid exposure exhibits reduced cancellous bone area and decreased trabecular width. Trabecular profiles can be entirely resorbed. Finally, glucocorticoid exposure decreases long-bone area and is associated with a reduction in the rate of bone formation. Bone density often increases after the glucocorticoid excess is corrected, even in patients with long-standing Cushing syndrome.

Hyperthyroidism may also lead to increased bone resorption and osteoporosis. The mechanism may be a direct effect of thyroid hormone on osteoclast activity. Excessive exogenous thyroid hormone replacement may also be associated with bone loss. However, the clinical significance of this relationship, as well as its association with fracture, is unclear. (*From* Weinstein *et al.* [12]; with permission.)

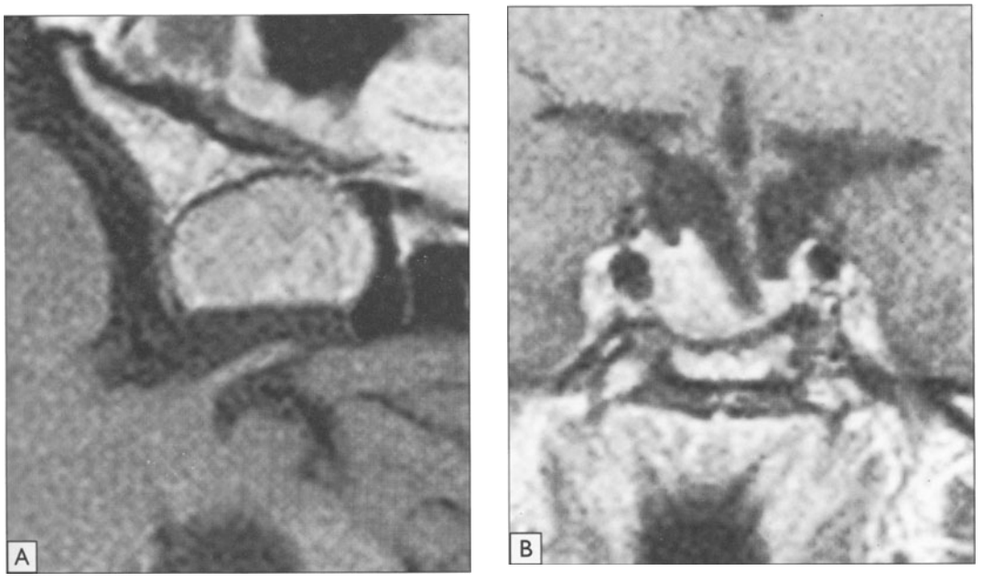



**FIGURE 11-23.** Magnetic resonance images (**A** and **B**) of an enlarged pituitary gland that is producing excess prolactin. Excess prolactin secretion, which is typical of prolactinomas, may be associated with increased bone resorption. This effect may be independent of the hypogonadism that often accompanies prolactinomas. In patients with low bone mass, bone loss, or unexplained fractures, magnetic resonance imaging of the pituitary may be diagnostic if elevated prolactin levels are detected.

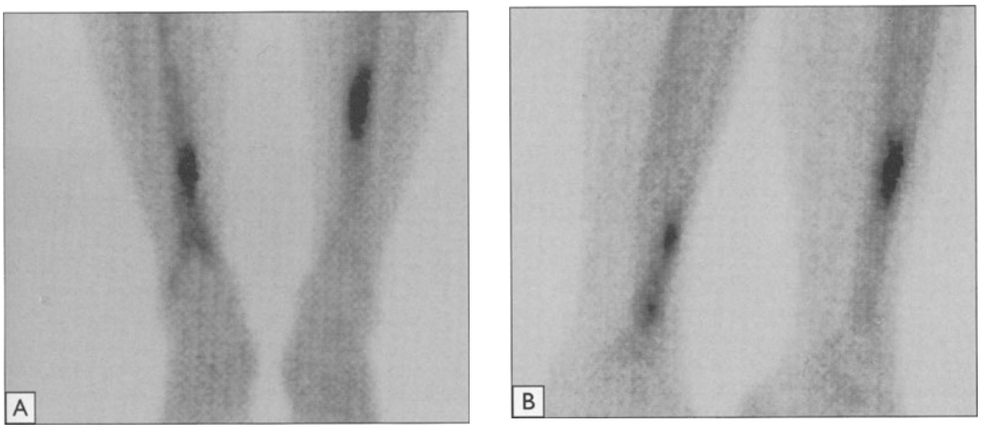



**FIGURE 11-24.** Radionuclide bone scan obtained from a young woman with hypomenorrhea, stress fractures, and painful shins but normal routine radiographs of the legs. **A**, Anterior view. **B**, Right lateral and left medial views. In both men and women, hypogonadism may lead to osteoporosis at any age. Postmenopausal osteoporosis is the most prevalent form of osteoporosis in women. Low testosterone concentrations in men may also be an etiologic factor for osteoporosis. Recently, osteoporosis in men has also been linked to deficiency of aromatase (the enzyme responsible for converting testosterone to estrogen). In men with unexplained low bone mass, elevations in circulating levels of follicle-stimulating hormone and luteinizing hormone, low concentrations of free or bioavailable testosterone, low plasma estradiol-estrone concentrations, or low insulin-like growth factor-1 levels suggest this enzymatic disorder. Androgen replacement does not correct the defect in these patients, and estrogen replacement may be required to prevent further bone loss.

Osteoporosis may also occur in young women and men with hypothalamic-pituitary dysfunction related to excessive exercise or eating disorders. In affected young women, amenorrhea or hypomenorrhea results from inadequate production of follicle-stimulating hormone and luteinizing hormone and bone mass is lost. Such patients often present with painful feet or tibial pain. Routine radiographs are often normal, but a bone scan confirms the diagnosis of stress fractures. It is important to emphasize that these women are losing bone systemically. Some of these women have a hip fracture as their first fracture. Bone density may not be extremely low in these cases, and bone fragility may be related to the high rate of bone turnover associated with gonadal deficiency and nutritional inadequacies.

**FIGURE 11-25.** Patient with acromegaly and vertebral fractures. Osteoporosis may be seen in patients with acromegaly, a body habitus that would not be expected to be associated with low bone mass. This association is probably related to the hypogonadism that occurs in patients with these pituitary tumors. Despite elevated growth hormone levels, gonadal insufficiency dominates the metabolic milieu of these patients.

## Osteoporosis Related to Pregnancy

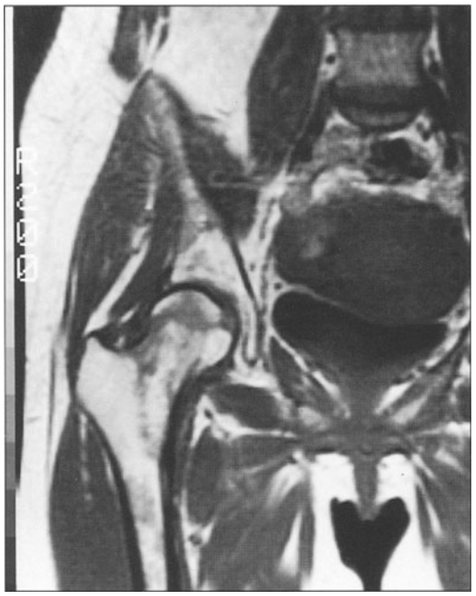


**FIGURE 11-26.** Magnetic resonance image of a pregnant woman's hip. Osteoporosis of the hip is a specific condition associated with pregnancy and lactation. The mottled decreased signal on a T1-weighted image of the femoral head distinguishes this condition from aseptic necrosis of the femur. Osteoporosis of pregnancy is painful, even without a fracture. It heals spontaneously after delivery or cessation of lactation [13].

## Osteoporosis Related to Nutritional Deficiency

**STATES OF NUTRITIONAL DEFICIENCY ASSOCIATED WITH OSTEOPOROSIS**

Poor calcium consumption
Vitamin D deficiency
Anorexia nervosa or bulimia
Deficiencies in vitamin K or vitamin C

**FIGURE 11-27.** States of nutritional deficiency associated with osteoporosis [14]. Osteoporosis, which is not accompanied by osteomalacia, has been described in populations with chronic low intake of dietary calcium. In fact, calcium replacement alone in late postmenopausal women may retard bone loss and reduce fractures. Although vitamin D deficiency is often associated with osteomalacia, patients with low vitamin D levels may also lose bone density and sustain fractures in the absence of osteomalacia. Vitamin D replacement may also reduce fractures in subsets of postmenopausal women. These effects are mediated by a combination of mechanisms, including positive calcium balance, reduction in bone turnover, and improvement of muscle tone and balance. Recent data indicate that vitamin K and vitamin C also have important roles in bone metabolism.

## Low Bone Mass Related to Osteomalacia and Osteogenesis Imperfecta

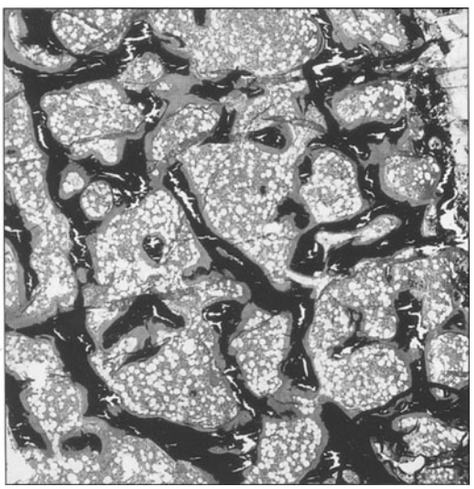


**FIGURE 11-28.** (see Color Plate) Histologic findings on bone biopsy specimen from a patient with osteomalacia. Low bone mass may also be associated with very different types of metabolic bone diseases, including osteomalacia and osteogenesis imperfecta. Osteomalacia is the accumulation of excess osteoid (nonmineralizing bone) caused by impaired mineralization of osteoid (thick pink outer layer on black calcified bone surface). This impairment can result from several clinical and pathophysiologic conditions. The strict quantitative histomorphometric criteria used to diagnose osteomalacia are 1) osteoid surface greater than 80%, 2) osteoid thickness greater than 14 μm, and 3) mineralization lag time of 100 days or more. In addition, there are subclassifications of "preosteomalacia" and "focal" osteomalacia with separate criteria; these conditions may be less severe and are related to lesser degrees of vitamin D deficiency. These alternative classifications of osteomalacia may simply represent different developmental stages of the disorder.

**CLINICAL CONDITIONS ASSOCIATED WITH OSTEOMALACIA**

- Malabsorption
- Chronic liver disease
- Hemigastrectomy
- Chronic hypophosphatemia
- Chronic hypophosphatemia or phosphaturia with inadequate 1,25-dihydroxyvitamin D levels (oncogenic osteomalacia or proximal renal tubular defects)
- Severe reduction in 25-hydroxyvitamin D levels
- Chronic metabolic acidosis
- Medications such as phenytoin sodium, phenobarbital, continuous high-dose etidronate therapy, excess fluoride
- Chronic renal failure

**FIGURE 11-29.** Clinical entities associated with osteomalacia. The most common causes of osteomalacia are conditions that result in vitamin D deficiency or hypophosphatemia. Low 25-hydroxyvitamin D concentrations are often seen in patients without osteomalacia. A spectrum of calcium metabolism disorders may be related to both the duration and the severity of vitamin D deficiency. Osteomalacia occurs more often in patients whose 25-hydroxyvitamin D values are less than 6 ng/mL. This level of reduction often leads to decreases in 1,25-dihydroxyvitamin D levels and osteoporosis. Levels of 25-hydroxyvitamin D greater than 12 ng/mL may still be associated with elevated circulating parathyroid hormone levels, which may aggravate bone loss. Osteomalacia can be present with normal vitamin D levels and normal bone alkaline phosphatase activity. The condition cannot be diagnosed by assuming that it is present in patients with elevated bone alkaline phosphatase activity and clinical entities that may be associated with osteomalacia [15].

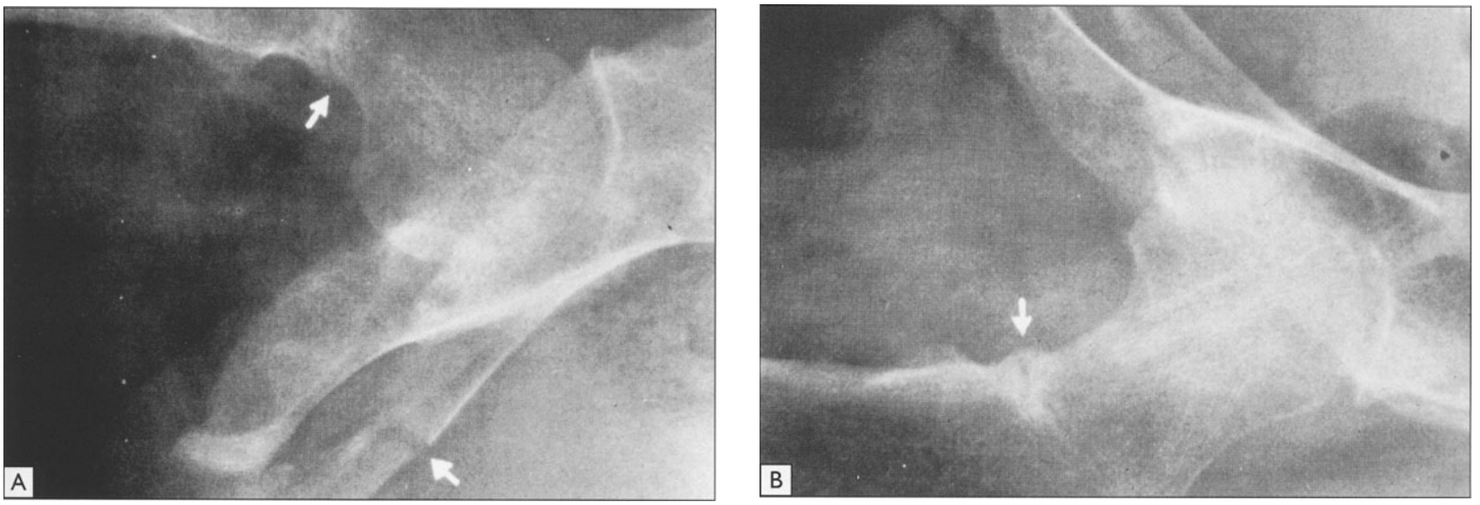



**FIGURE 11-30.** Looser's zones (**A** and **B**) on radiography. These lines occur only in advanced cases of osteomalacia. The diagnosis can be made only by quantitative bone histomorphometry.

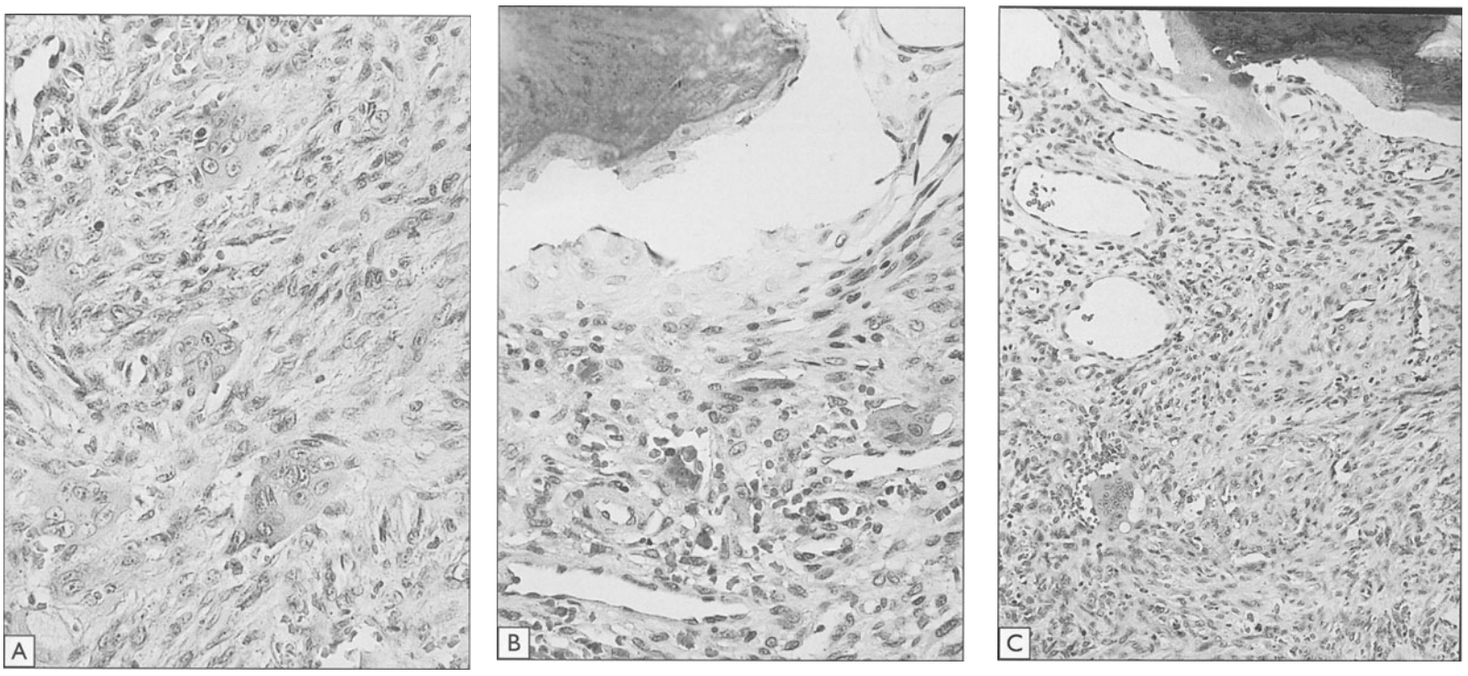



**FIGURE 11-31.** (see Color Plate) Histologic characteristics of a tumor associated with oncogenic osteomalacia. Bone biopsy should be considered in clinical situations related to osteomalacia, particularly in patients with fractures or chemical abnormalities that are associated with oncogenic osteomalacia [16]. Establishing the correct diagnosis in these cases is important because pharmacologic treatment (phosphorus and 1,25-dihydroxyvitamin D replacement) must be tailored to the condition. Clinicians should continue to search for the mesenchymal cell line tumor that will appear months to years after diagnosis. **A**, Multinucleated giant cells admixed with spindle-shaped mesenchymal cells. Vascular spaces are filled with blood and yellow-brown pigment, most compatible with hemosiderin. **B**, Giant cells and mesenchymal cells with a focus of ossification. **C**, A lower magnification of **B**, which also shows prominent dilated vascular spaces.

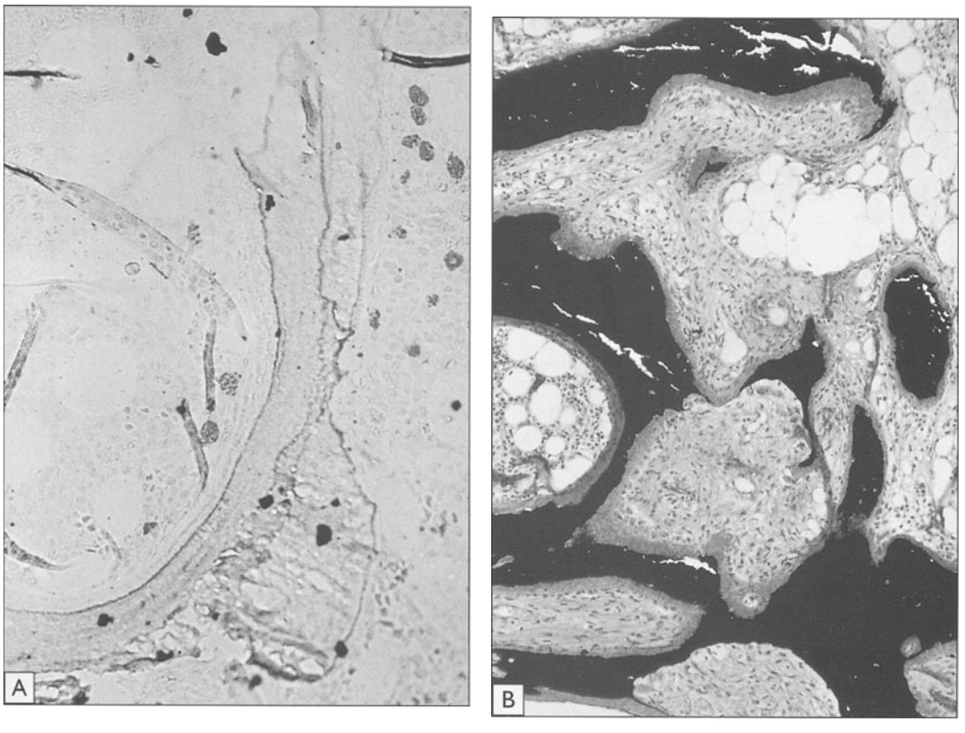



**FIGURE 11-32.** (see Color Plate) Bone biopsy specimens in patient with chronic renal failure. Bone biopsy may be the only method of determining whether the observed hypercalcemia or elevated alkaline phosphatase level is related to osteomalacia, aluminum accumulation, or hyperparathyroidism. This determination is particularly important if deferoxamine therapy, long-term 1,25- dihydroxyvitamin D treatment, or surgical parathyroidectomy is being considered. In some patients, serum parathyroid hormone levels and alkaline phosphatase activity may help distinguish between hyperparathyroidism and aluminum bone disease. However, sufficient overlap exists in individual patients that bone histologic characteristics become the definitive way of making a specific diagnosis. **A**, Aluminum, shown in red, covering osteoid surfaces. **B**, Features of osteitis fibrosa cystica: fibrosis of the bone marrow, excess bone resorption shown by scalloping, and abundant osteoid shown by the thick pink layer.

The patient shown in this figure was receiving long-term dialysis and had hypercalcemia and intact parathyroid hormone concentrations that were eight times the upper limit of normal. Aluminum covered 100% of this patient's osteoid surfaces [17]. Proceeding with parathyroidectomy just on the basis of the chemical aberrations, before aluminum chelation, would have been a serious error because of the high likelihood of postoperative aluminum-related adynamic bone disease, a crippling disorder.

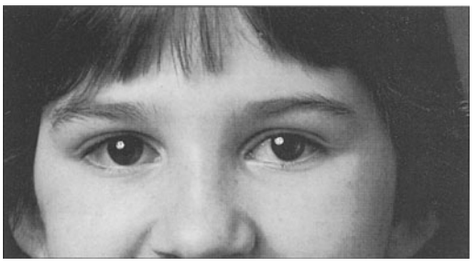
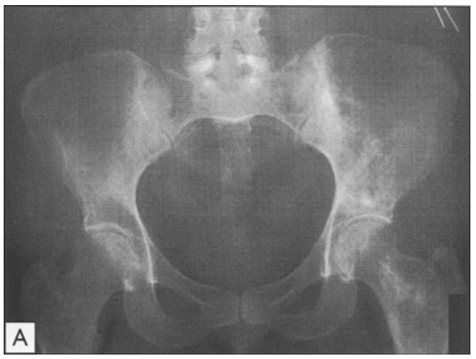


**FIGURE 11-33.** (see Color Plate) Blue sclera in a child with osteogenesis imperfecta. Low bone mass and fractures are seen in patients with osteogenesis imperfecta. In children with this disorder, it is often difficult to discriminate osteogenesis imperfecta from idiopathic juvenile osteoporosis [18]. If the patient has blue sclera, the diagnosis of osteogenesis imperfecta is clear. Tissue culture of skin biopsy specimens may also be helpful in diagnosing osteogenesis imperfecta.

## Diseases That Might Be Detected in the Clinical Assessment of Patients with Metabolic Bone Disease



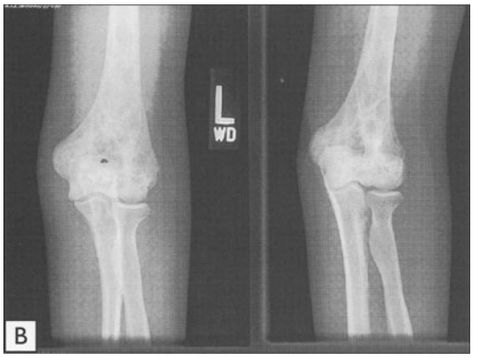




**FIGURE 11-34. A**, Paget's disease of the left side of the ilium and left proximal femur. The scalloping appearance of sclerotic bone intermixed with radiolucent osteolytic areas is a classic appearance of the skeleton with Paget's disease. Paget's disease is a radiographic—not bone scan—diagnosis. Bone scans, however, are also "positive" in patients with Paget's disease, as they may also be in patients with osteoporosis after a recent fracture, metastatic bone disease, and fibrous dysplasia. **B,** Paget's disease of the humerus involving the joint. This skeletal site of Paget's disease has a higher risk of development of osteogenic sarcoma than that of other skeletal sites that may have Paget's disease.

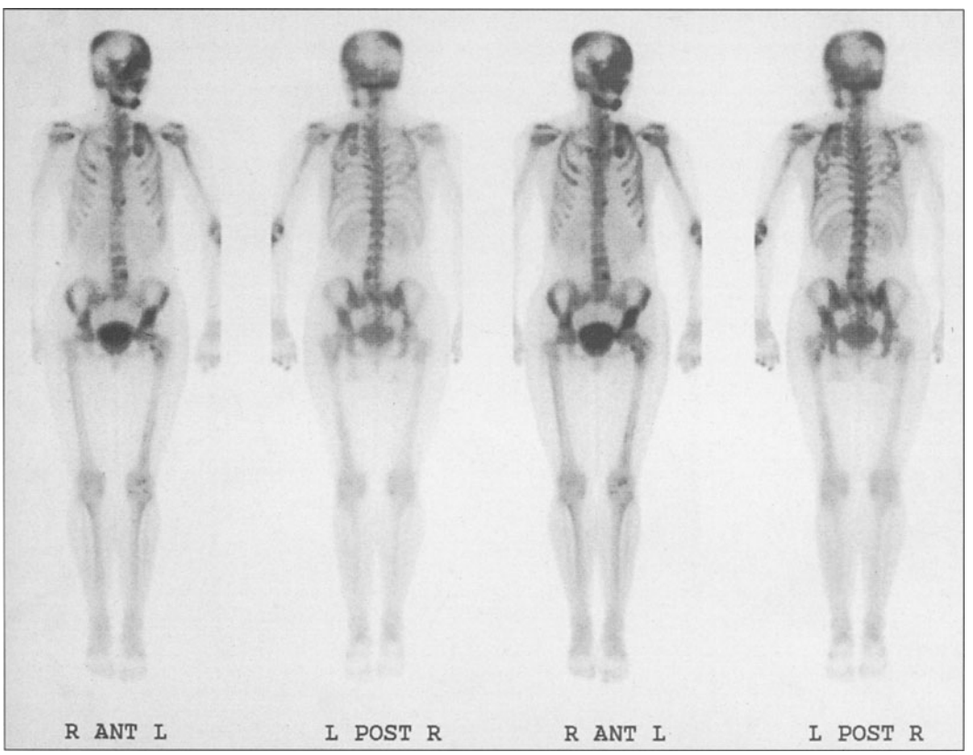



**FIGURE 11-35.** Bone scan of a woman with fibrous dysplasia involving nearly the entire left side of her skeleton. Routine radiographs confirmed the diagnosis of fibrous dysplasia, which differs from Paget's disease on x-ray film by a more prevalent component of thin cortices and a ground-glass appearance of bone. However, the x-ray lesions are occasionally lobulated, with trabecular areas of radiolucency that may be difficult to distinguish from lesions in Paget's disease. In the assessment of patients with suspected osteoporosis or skeletal pain, bone scans and radiographs are often obtained. A "hot" bone scan is nonspecific and is normal in osteoporosis unless there has been a recent fracture, usually having occurred less than 3 to 6 months previously. A positive bone scan needs to be followed-up with routine radiographs of the skeletal areas to help distinguish between the diseases that may be associated with a positive bone scan. In many cases, magnetic resonance imaging needs to be done to discriminate the sclerotic x-ray appearance of Paget's disease and fibrous dysplasia from some malignancies that may have a sclerotic component, such as prostate cancer.

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12

# GLUCOCORTICOID-INDUCED OSTEOPOROSIS

*Lorraine A. Fitzpatrick*

Skeletal decalcification was recognized as a feature of Cushing disease as early as 1932. With the isolation of cortisol, the anti-inflammatory, antineoplastic, and immunosuppressive properties of glucocorticoids have been useful for treating many diseases. Patients exposed to long-term glucocorticoid therapy have distinct clinical features associated with the suppression of the hypothalamic-pituitary-adrenal axis [1]. Glucocorticoid-induced osteoporosis is probably the most common cause of secondary osteoporosis. Although the true incidence of osteoporosis in this population remains unknown, patients receiving high-dose glucocorticoid therapy experience rapid bone loss and vertebral compression fractures that can occur within weeks to months of initiation of therapy [2]. Overall, 30% to 35% of patients receiving glucocorticoid therapy sustain vertebral crush fractures and have a 50% increased risk of hip fracture [3].

The bone loss caused by excess glucocorticoids is diffuse and affects both the cortical and axial skeleton. Glucocorticoids damage trabecular bone to a greater extent than cortical bone, perhaps because of the greater surface area of trabecular bone. The osteopenia is caused by several mechanisms: suppression of osteoblast function, inhibition of intestinal calcium absorption leading to secondary hyperparathyroidism, and increased osteoclast-mediated bone resorption. The role of parathyroid hormone (PTH) in the pathogenesis of glucocorticoid-induced osteoporosis has been reexamined. The classic model of glucocorticoid-induced osteoporosis suggests that there is a compensatory increase in PTH due to the decrease in calcium absorption by the intestine and increased urinary calcium excretion. Some studies also suggest that vitamin D deficiency (or insufficiency) is another contributory factor. There are data that contradict this hypothesis, because in some cases PTH secretion is not stimulated by glucocorticoid treatment [4]. Bone resorption is promoted by the direct stimulation of renal excretion of calcium by glucocorticoids and hypogonadism associated with the suppressive effects of glucocorticoids.

The minimum glucocorticoid dose associated with rapid bone loss is not well established. Patients with juvenile chronic arthritis ingesting a cumulative prednisone dose of 5 mg sustain vertebral fractures [5]. In adults, as little as 2.5 mg of prednisolone is associated with bone loss [4,6]. Even inhaled glucocorticoids, the most commonly used medications for long-term treatment of patients with asthma, have been evaluated for their role in glucocorticoid-induced bone loss. The number of puffs per year of use of inhaled glucocorticoids is associated with a decline in bone mineral density (BMD) at the hip in premenopausal women [7]. Studies that evaluate mineral density of trabecular bone indicate that loss of this type of bone is significantly greater than loss of cortical bone, probably because of the differential effect of glucocorticoid therapy on trabecular versus cortical bone. Traditional risk factors associated with osteoporosis also influence glucocorticoid-induced osteoporosis. Retrospective analysis also suggests that certain factors are associated with increased risk of glucocorticoid-induced bone loss. Osteoporosis is more severe in patients younger than 15 years or older than 50 years of age and in postmenopausal women [5,8]. In older, immobilized, or postmenopausal patients, a pre-existing low level of bone mass may lead to rapid development of clinically significant osteopenia. In the younger patient, a higher rate of bone turnover results in more rapid bone loss. The improved longevity in transplant recipients has also raised issues about glucocorticoid-associated bone loss. The additional immunosuppressive agents that these patients are prescribed makes the relative contribution of each agent to bone loss difficult to assess. The incidence of fracture rates range from 8% to 65% during the first year after transplan-

tation, and rates of fracture and bone loss are greatest in the first 6 to 12 months after transplantation [9]. Other risk factors include low body mass index [10]; disorders associated with interleukin-1 production, such as rheumatoid arthritis; and the general osteoporosis risk factors.

Recently, several studies have furthered our understanding of the cellular and molecular mechanisms responsible for glucocorticoid-induced bone loss. Glucocorticoids decrease osteoblast function directly and indirectly through the modulation of growth factor expression, receptor binding, or binding protein levels [11]. The ability of glucocorticoids to suppress bone formation by inhibiting osteoblastogenesis and increasing osteoblast apoptosis has been established. However, the role of bone resorption in the initial rapid phase of bone loss has been less well understood. In murine osteoclast cultures, glucocorticoids prolonged the baseline survival of osteoclasts and antagonized bisphosphonate-induced caspase activation and apoptosis. In cancellous bone, the number of osteoclasts increased in the murine model even though osteoclast progenitor number was reduced. Bisphosphonate administration in this model prevented glucocorticoid-induced osteoblast apoptosis. This study explains the early loss of bone in the presence of glucocorticoids and confirms that it is caused by extension of the lifespan of pre-existing osteoclasts, which is not preventable by bisphosphonates [12].

At the molecular level, glucocorticoids regulate gene expression by transcriptional and post-transcriptional mechanisms. The transcriptional effects are mediated by the glucocorticoid hormone receptor, either through activation or repression of gene expression. Select cytokines such as interleukin (IL)-6 and IL-11 can increase and decrease glucocorticoid receptor levels, respectively. Interest has also focused on glucocorticoid effects on the receptor activators of the nuclear factor-κB ligand (RANKL)-osteoprotegerin (OPG) axis. Glucocorticoids enhance RANKL and colony stimulating factor-1 expression, and inhibit OPG production, resulting in an induction of osteoclastogenesis. These findings produce the mechanism for early increase in bone resorption in the presence of glucocorticoids.

The degree of bone loss is related to the dose and duration of glucocorticoid therapy. At the time of initiation of glucocorticoid therapy, there is a rapid phase of bone loss followed by a slower but continuous decline of BMD. This phase of less decline can be misinterpreted as a stabilization of BMD and provide a false sense of reassurance to the patient and physician. These patients are still at added risk for fractures and aggressive therapy is warranted. Biochemical markers are altered in patients on glucocorticoids. Serum osteocalcin and alkaline phosphatase levels, markers of bone formation, are low. At the same time, markers of bone resorption, such as urinary free deoxypyridinoline excretion, are suppressed.

Prevention and treatment of glucocorticoid-induced osteoporosis is the ultimate goal in the management of these patients. Because glucocorticoids decrease intestinal calcium absorption and increase urinary calcium excretion, supplemental calcium and vitamin D or thiazide therapy may be warranted. Replacement of sex steroid hormones in both men and women is recommended, although prospective data on its impact on fracture risk is lacking. Two bisphosphonates, alendronate and risedronate, are approved for glucocorticoid-induced osteoporosis in men and women. Alendronate decreased the incidence of vertebral fractures after 2 years of therapy and increased BMD in glucocorticoid-treated patients. With risedronate, in a group targeted for prevention, BMD did not decline in patients treated with risedronate, compared with patients receiving calcium-containing placebo. In a treatment study with risedronate, BMD was significantly increased in the risedronate-treated group and a reduction in vertebral fracture was observed when both treatment and prevention data were pooled. Prospective trials on the use of intravenous ibandronate and pamidronate have demonstrated increases in vertebral and hip BMD in patients with glucocorticoid-induced osteoporosis, although these are not yet approved therapies. Newer data on the use of recombinant human PTH (1-34) are encouraging and suggest a potential role for this anabolic hormone in the treatment of this disorder [13].

## Epidemiology and Risk Factors

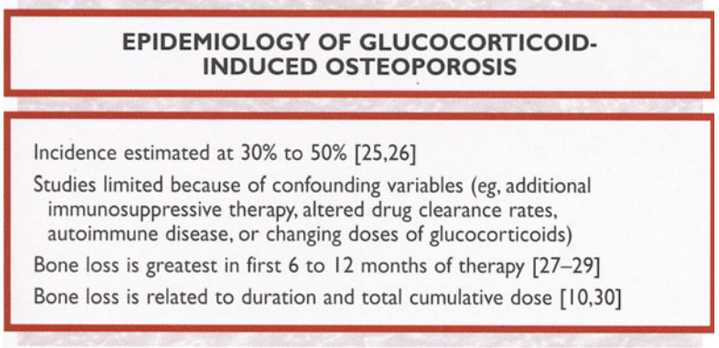



**FIGURE 12-1.** Epidemiology of glucocorticoid-induced osteoporosis.

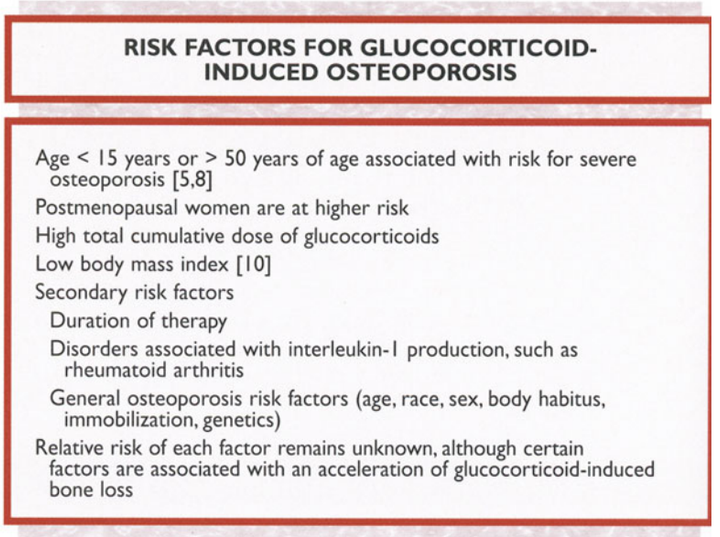



**FIGURE 12-2.** Risk factors for glucocorticoid-induced osteoporosis.

## Pathophysiology

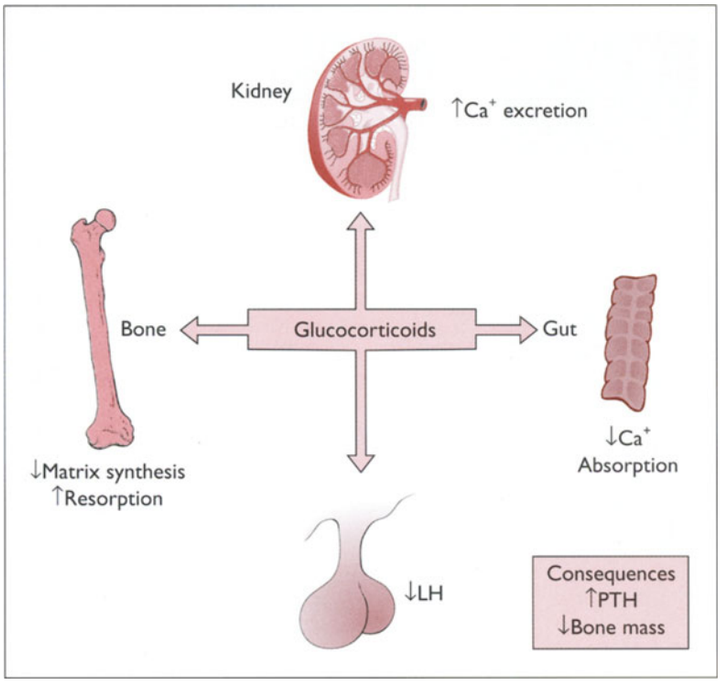
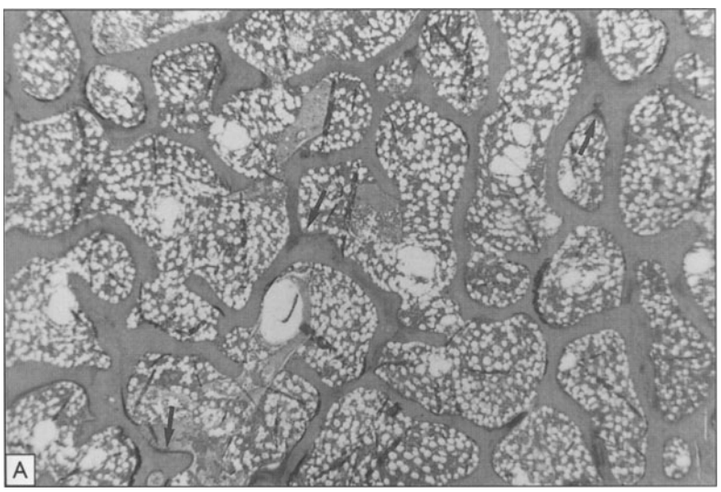



**FIGURE 12-3.** The pathophysiology of glucocorticoid-induced bone loss. Several interrelated factors affect mineral metabolism in patients with an excess of endogenous or exogenous glucocorticoids. Glucocorticoids directly affect the bone, alter calcium absorption from the intestine, change the ability of the kidney to reabsorb calcium, and inhibit gonadal hormone secretion. Secondary hyperparathyroidism has been documented in patients receiving glucocorticoid therapy.

Intestinal absorption of calcium determines the amount of substrate available to meet the needs of bone remodeling. Glucocorticoids decrease net intestinal calcium absorption by an unknown mechanism [14]. Glucocorticoids may alter vitamin D metabolism; this would also inhibit calcium absorption. Bone constantly undergoes remodeling and can be greatly affected by administration of glucocorticoids [15]. Suppression of bone formation is the major impairment in bone physiology caused by glucocorticoids [16]. Glucocorticoids directly inhibit differentiation of preosteoblasts and alter the oncoproteins that regulate the genes for alkaline phosphatase, osteocalcin, and other growth factors [17,18]. Calcium kinetic studies support the hypothesis that glucocorticoids enhance bone resorption [19]. At the level of the kidney, glucocorticoids enhance calcium excretion.

Glucocorticoids can alter levels of gonadal hormones in both men and women. Glucocorticoids reduce testosterone levels in men [20,21] and interfere with normal ovulation in women [22]. Serum follicle-stimulating hormone and luteinizing hormone (LH) are suppressed by exogenous glucocorticoid administration. The cause of secondary hyperparathyroidism is attributable to the decrease in calcium absorption, and direct action of glucocorticoids on the parathyroid gland has been documented [23]. However, this hypothesis has been recently questioned [24]. PTH—parathyroid hormone.

## Bone Histomorphometry



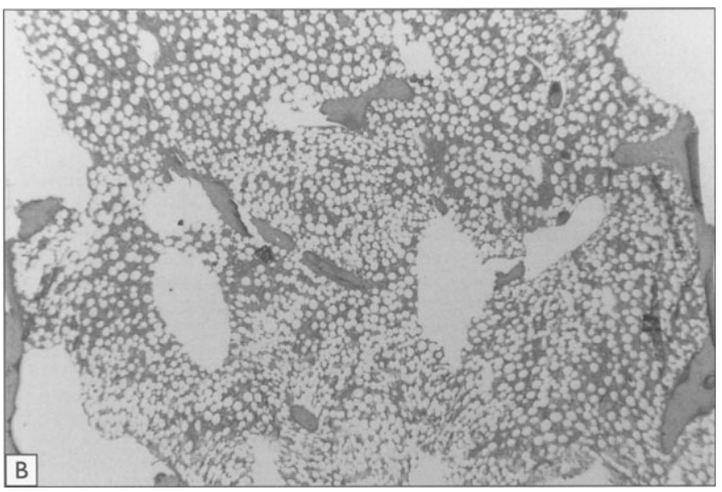




**FIGURE 12-4.** (see Color Plate) **A,** Normal trabecular bone from a 30-year-old patient. Note the thick, serpiginous trabecular plates with excellent connectivity. Arrows indicate areas of osteoid, consistent with bone formation. **B,** Severe osteoporosis in a 30-year-old patient receiving long-term glucocorticoid therapy. Multiple isolated bone islands are present, and little evidence of bone formation is noted. Histomorphometrically, dynamic measures of bone formation are profoundly reduced, indicating that remodeling has been uncoupled. The larger surface area of trabecular bone suggests that it is more affected by glucocorticoids than is cortical bone; however, reduction in cortical bone volume can be seen. It is estimated that 30% loss of bone occurs during each remodeling cycle in patients receiving glucocorticoid therapy.

## Physical Findings

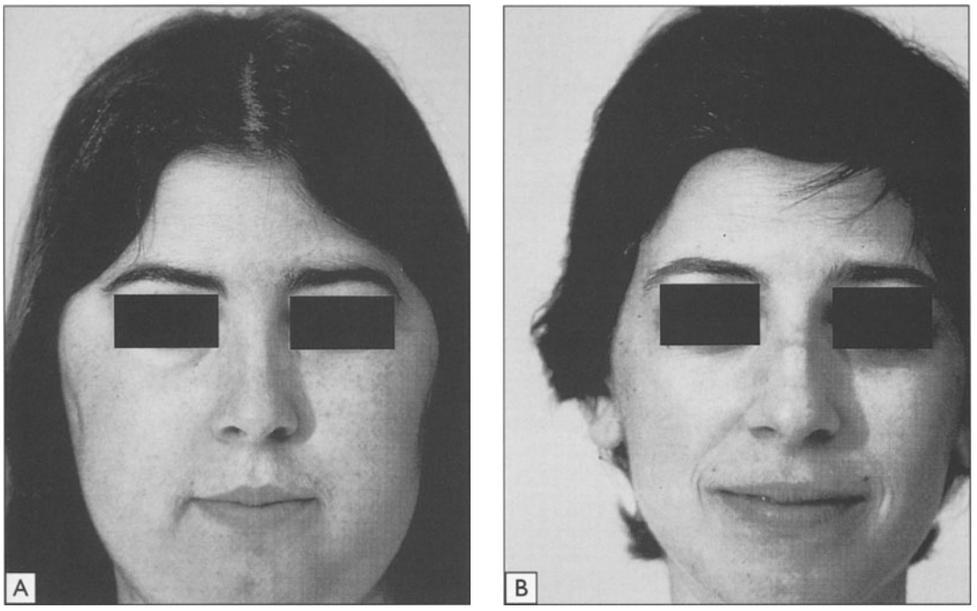



**FIGURE 12-5.** Symptoms and physical findings that can identify patients with excessive glucocorticoids. Increased deposition of fat is one of the earliest signs to occur in almost all patients (**A**). Fat distribution is increased in the peritoneal cavity, mediastinum, and, as shown here, subcutaneous sites on the face and neck. The "moon facies" with increased fat in the supraclavicular or temporal fossae and dorsocervical area ("buffalo hump") are rarely seen in normal individuals. Filling of the temporal fossae may prevent eyeglass frames from fitting properly. Rarely, long-term exogenous steroid use results in fat accumulation in the epidural space and can cause neurologic deficits. Alterations in fat distribution resolve when glucocorticoid therapy is stopped (**B**).

## Radiographic Diagnosis

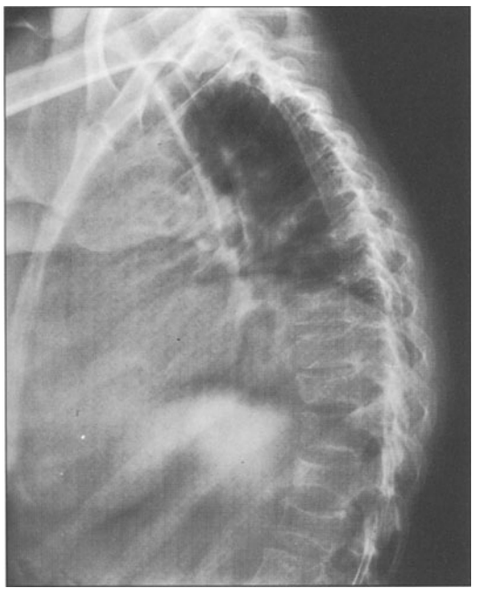


**FIGURE 12-6.** Osteopenia on spine radiography. High circulating levels of glucocorticoids, either endogenous or exogenous, cause marked loss of bone mineral density. Both cortical and cancellous bone is lost, and vertebral collapse, as shown in this figure, is not uncommon.

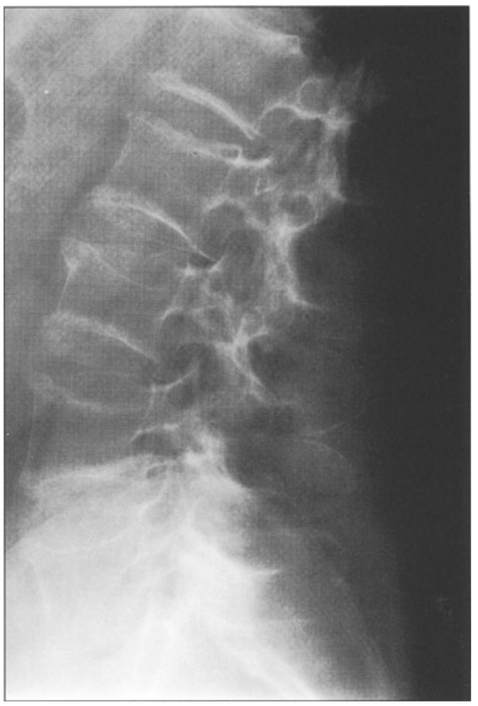
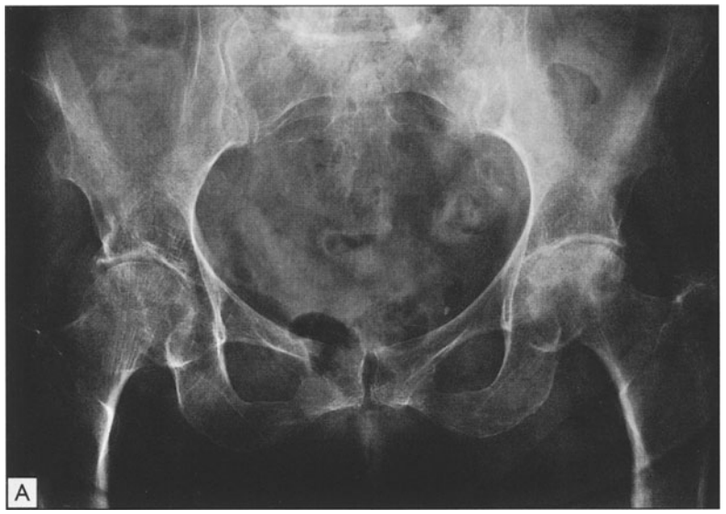


**FIGURE 12-7.** Radiograph of a 50-year-old woman who has been receiving daily steroid therapy for systemic lupus erythematosus for 2 years. Osteoporosis with ballooning of the thoracic and lumbar interspaces is present. Sclerosis of the vertebral endplates is also noted. The patient also had avascular necrosis of the right femoral head.



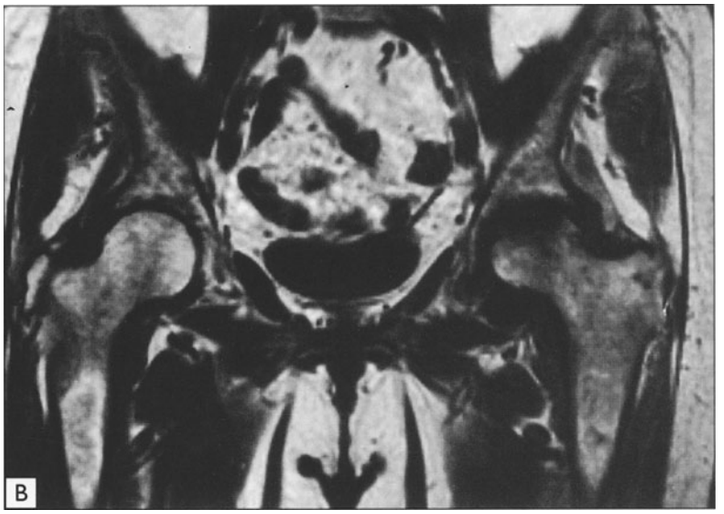




**FIGURE 12-8.** Radiograph and magnetic resonance imaging (MRI) scan of the hip. The left hip film (**A**) shows irregularity and sclerosis of the left femoral head with collapse of the articular cortex. The T1-weighted coronal MRI of the hips (**B**) shows a region of decreased signal in the superior portion of the left femoral head. The plain film and MRI finding are characteristic of avascular necrosis of the left hip. By using MRI, the death of marrow fat cells can be detected as early as 12 to 48 hours after its onset. Plain film findings may appear months after the onset of clinical symptoms.

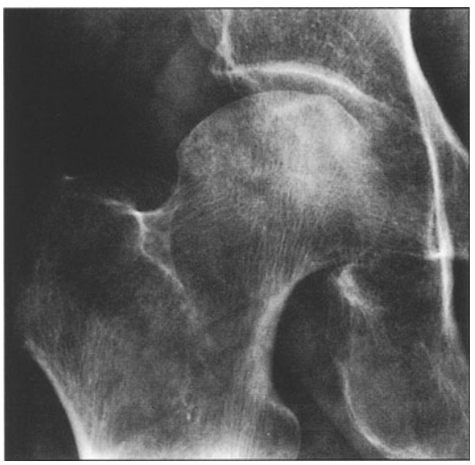


**FIGURE 12-9.** Osteonecrosis of the right femoral head. Sclerosis of the right femoral head with irregularity of the superior articular surface is consistent with avascular necrosis in this 71-year-old woman receiving steroids. Complications of avascular necrosis include secondary degenerative arthritis, intra-articular osteochondral loose bodies, and cystic degeneration.

**DIFFERENTIAL DIAGNOSIS OF AVASCULAR NECROSIS OF THE FEMORAL HEAD**

| | |
|---|---|
| Trauma | Dysbaric conditions (Caisson disease) |
| Hemoglobinopathies | Collagen vascular diseases |
| Exogenous or endogenous steroid use | Gaucher disease |
| Renal transplantation | Gout |
| Alcoholism | Irradiation |
| Pancreatitis | Synovitis |

**FIGURE 12-10.** Differential diagnosis of the femoral head.

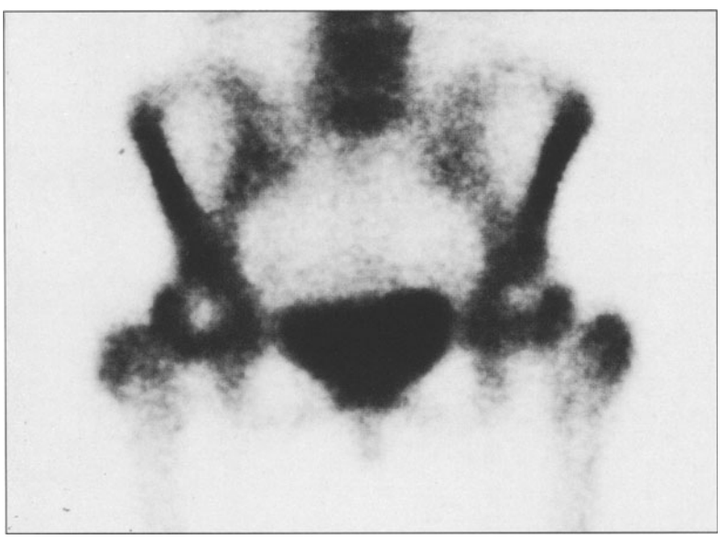


**FIGURE 12-11.** Bone scan of a 53-year-old woman with a history of systemic lupus erythematosus and hip pain who had been receiving steroids for many years. The bone scan shows focal areas of increased uptake in the proximal right humerus and both femoral heads. The areas of increased uptake in the femoral heads surround photopenic defects. The appearance of uptake is classic for avascular necrosis.

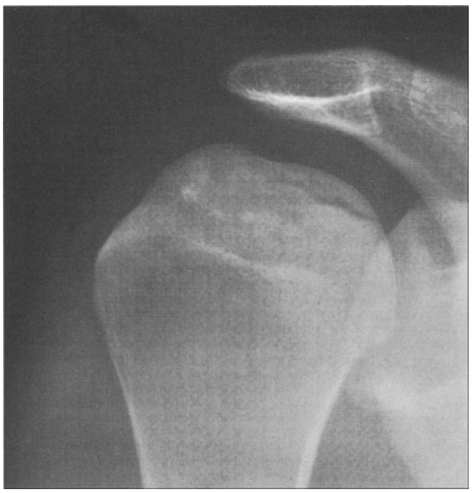


**FIGURE 12-12.** Radiograph of a 26-year-old man with right shoulder pain who had been receiving long-term glucocorticoid therapy for systemic lupus erythematosus. The film shows avascular necrosis of the right humeral head with collapse, subchondral fracture, and sclerosis.

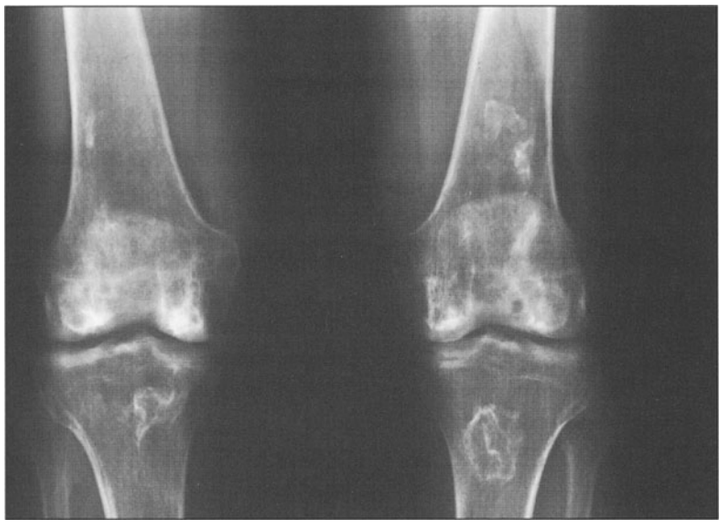


**FIGURE 12-13.** Radiograph of a 42-year-old man with a history of high-dose steroid therapy given for hepatitis. Regular but discrete areas of increased density can been seen in the medullary region of both distal femurs and proximal tibias; these areas are most pronounced at the periphery of the lesions. This finding is consistent with multiple bone infarctions secondary to exogenous steroid use. The pathogenesis of steroid-induced infarction is not known, but attention has focused on the presence of microscopic fat emboli in the end arteries of bone and other organ systems.

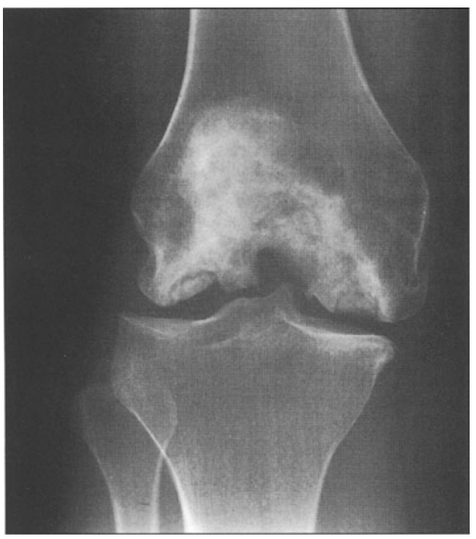


**FIGURE 12-14.** Radiograph of a 30-year-old woman with Crohn's disease who has been receiving prednisone for 15 years. Extensive avascular necrosis involving the femoral condyle is present. The femoral head, humeral head, distal femur, and proximal tibia are common sites of steroid-induced avascular necrosis.

**STAGING OF ISCHEMIC NECROSIS OF THE FEMORAL HEAD**

| Stage | Findings |
|---|---|
| 0 | Suspected necrosis but no clinical findings; normal radiographs and bone scan |
| I | Clinical findings, normal radiographs, and abnormal bone scan |
| II | Osteopenia, cystic area, and bone sclerosis on radiographs |
| III | Crescent sign and subchondral collapse without flattening of the femoral head on radiographs |
| IV | Flattening of the femoral head and normal joint space on radiographs |
| V | Joint space narrowing and acetabular abnormalities on radiographs |

**FIGURE 12-15.** Staging of avascular necrosis of the femoral head.

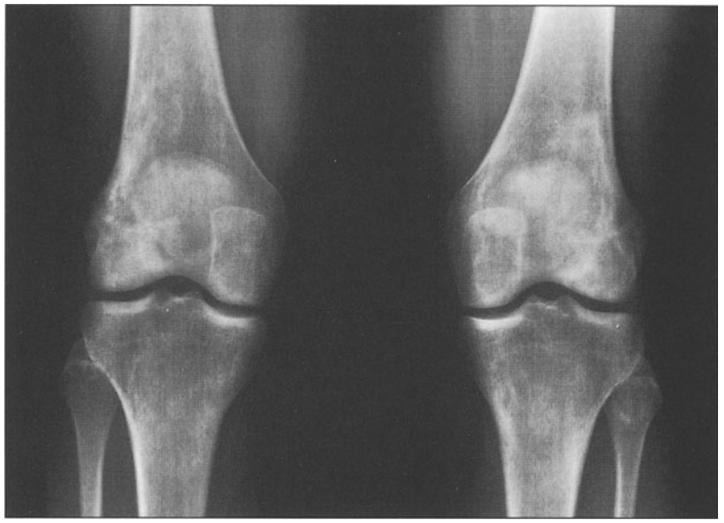
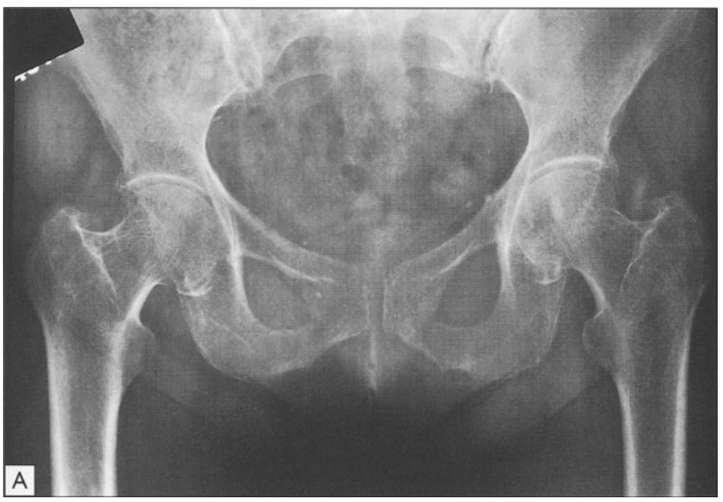
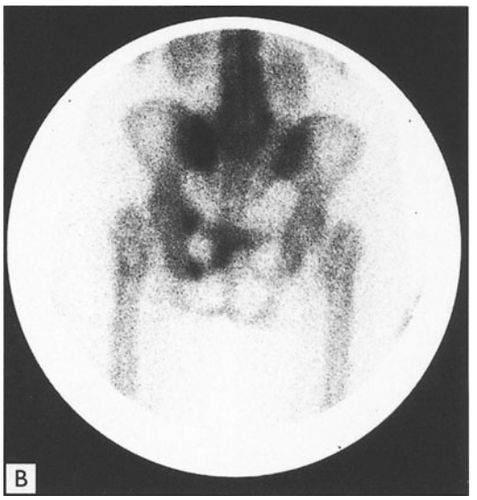


**FIGURE 12-16.** Knee radiographs of a 26-year-old woman with systemic lupus erythematosus receiving prednisone therapy. The film shows symmetric infarctions around both knees with mottled appearance and serpentine sclerosis.

## Bone Scans



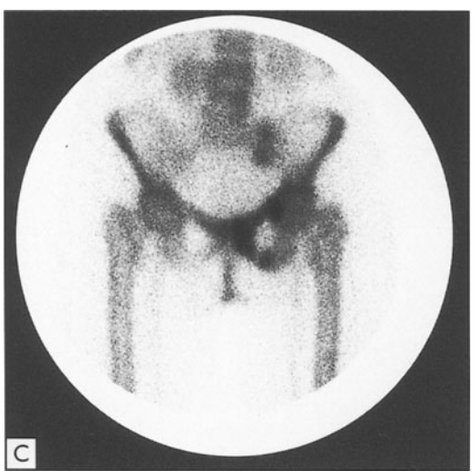




**FIGURE 12-17.** Bone scan and radiograph of the pelvis in a 73-year-old woman receiving glucocorticoids who experienced bilateral hip pain. The initial radiograph of the pelvis (**A**) showed slight sclerosis at the site of the fractures. This was confirmed on bone scan, which revealed foci of increased uptake in the superior and inferior left pubic rami, left pubic bone, and the left sacroiliac region (**B** and **C**).

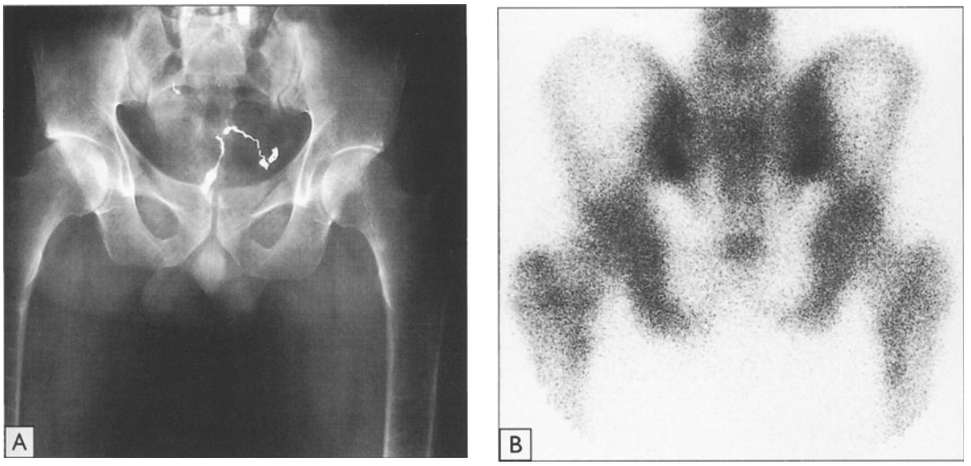



**FIGURE 12-18.** Radiograph (**A**) and bone scan (**B**) of a 34-year-old man with a history of Crohn's disease and long-term steroid use. The patient's short bowel syndrome also contributes to decreased calcium absorption. Both radiograph and bone scan showed bilateral stress fractures in the region of the lesser trochanter. The bone scan was positive before the plain film revealed the stress fractures. Stress fractures of the hip are particularly dangerous because they can become displaced fractures.

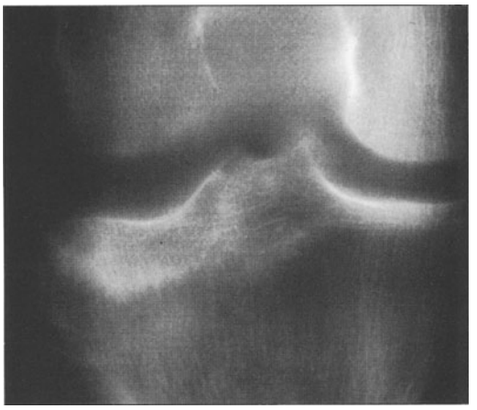


**FIGURE 12-19.** Knee radiograph indicating osteopenia and faint linear band sclerosis at the right lateral proximal tibia. This is consistent with a compression or stress fracture in the right lateral tibial plateau.

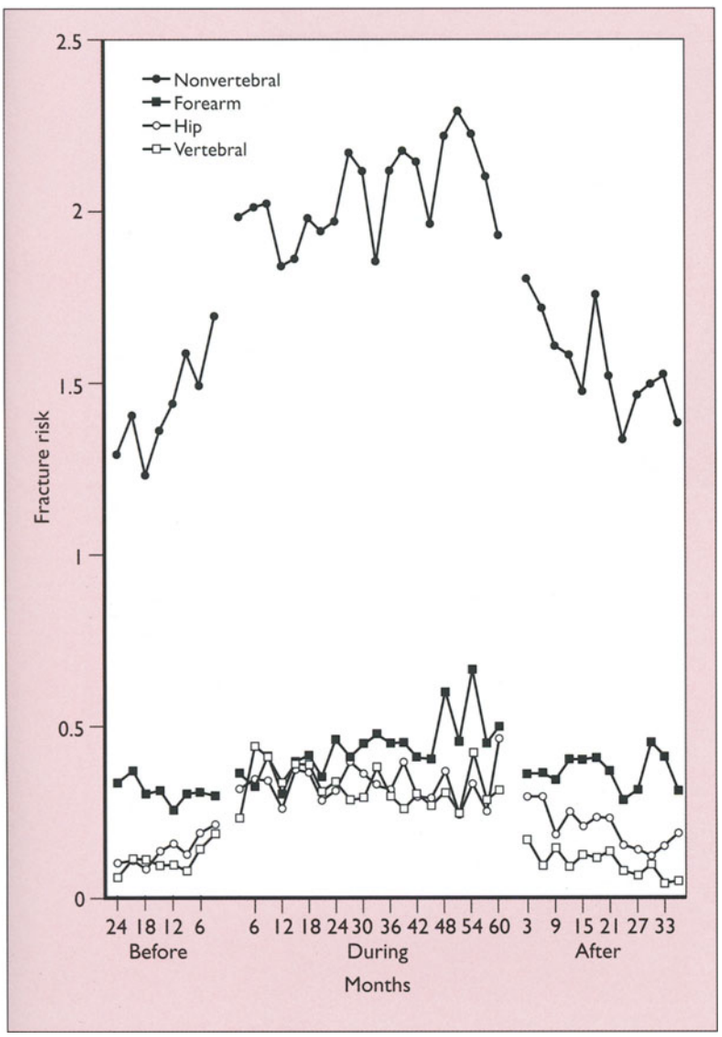



**FIGURE 12-20.** Mechanism of glucocorticoid-induced bone loss and fractures. In a retrospective study of a large number of patients treated with glucocorticoids, Van Staa *et al.* [31] demonstrated that there appears to be a rapid increase (within months) in fracture risk when treatment is begun and a similarly rapid decrease in fracture risk with discontinuation of therapy. The effects of glucocorticoids that are responsible for these findings are unknown, but have been speculated to include increases in bone resorption, increased osteoblast and osteocyte apoptosis, and an increase in the risk of falls. Clearly, these results also emphasize the need to prevent the adverse effects of glucocorticoids early in the course of therapy.

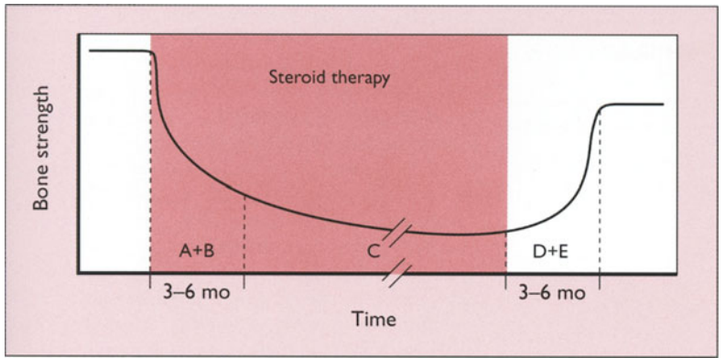



**FIGURE 12-21.** A model of the effects of glucocorticoids on bone. Manolagas [32] proposed that there are several stages in the response of bone to supraphysiologic doses of glucocorticoids, comprising an initial rapid reduction in bone strength related to increased bone resorption and osteocyte apoptosis, followed by a slower phase of bone defect accumulation due to suppressed bone remodeling. If glucocorticoids are stopped, there is a reversal of those abnormalities and an increase in bone strength and density. Prominent in the induction of the abnormalities in bone remodeling is the effect of glucocorticoids on bone cell apoptosis. Weinstein *et al.* [33] showed that osteoblast and osteocyte cell death was accelerated in glucocorticoid-treated animals and humans. As a result, bone formation is decreased and bone integrity is compromised. Glucocorticoids also appear to reduce osteoclast apoptosis, thus enhancing bone resorption and further promoting a negative bone balance [34]. The model illustrated here suggests that the ideal therapy for glucocorticoid-induced osteoporosis would include measures to both reduce excessive bone resorption and prevent or reverse bone cell apoptosis. Bone cell apoptosis has also been speculated to be important in the pathogenesis of glucocorticoid-induced avascular necrosis [34].

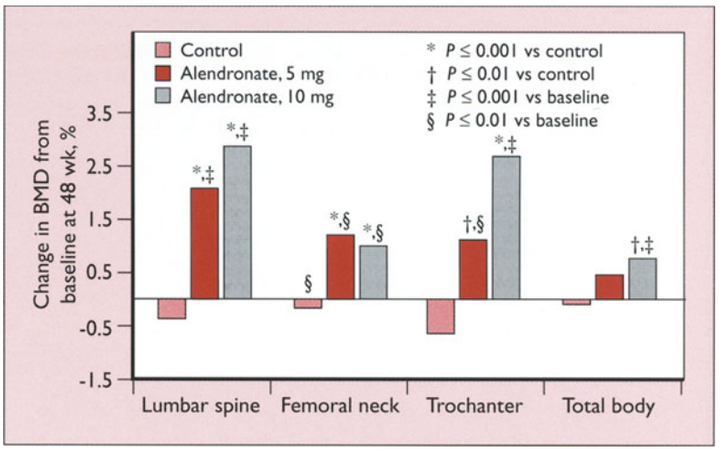



**FIGURE 12-22.** The effect of alendronate on bone density in patients receiving glucocorticoids. In patients who have glucocorticoid-induced osteoporosis, bisphosphonates appear to be quite effective in preventing bone loss and actually increasing bone density. In this study, Saag *et al.* [35] compared the effectiveness of alendronate (5 or 10 mg/d) versus placebo in a group of women and men who had been receiving glucocorticoid therapy. About half of the patients had been on glucocorticoids for more than 12 months. Despite the fact that all participants also took calcium and vitamin D supplements, those who received placebo tended to lose bone. Those who received alendronate increased bone density. Similar results are achieved with other oral or parenteral bisphosphonates. There are also fewer vertebral fractures in bisphosphonate-treated subjects [36,37]. Postmenopausal women tend to suffer the most when receiving glucocorticoid therapy, perhaps because of their sex steroid deficiency and tendency to have low bone mass before glucocorticoid therapy is begun. These patients may gain particular benefit from bisphosphonate treatment. BMD—bone mineral density.

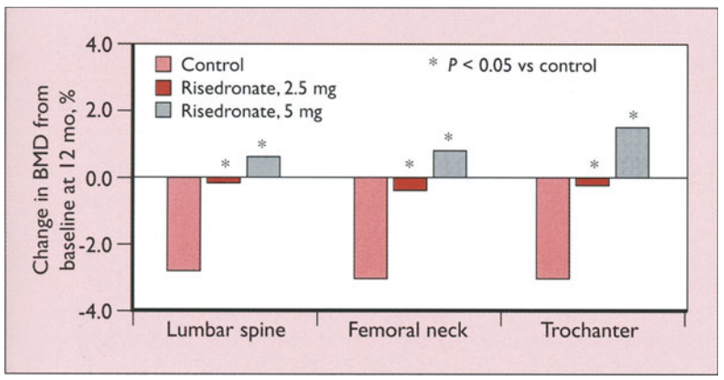



**FIGURE 12-23.** The effect of risedronate on bone density in patients starting glucocorticoids. Bisphosphonate treatment is quite effective in preventing the bone loss that often occurs when patients start glucocorticoid treatment. In these studies, Cohen *et al.* [38] began risedronate (2.5 or 5 mg/d) or placebo in patients who were starting glucocorticoid therapy for a variety of inflammatory disorders. All participants also received calcium and vitamin D supplements. Those taking risedronate were protected from bone mineral loss. In patients who are starting long-term supraphysiologic glucocorticoid therapy, simultaneous bisphosphonate therapy should be routinely considered, especially if bone mineral density (BMD) is already low or there are other risk factors for bone loss.

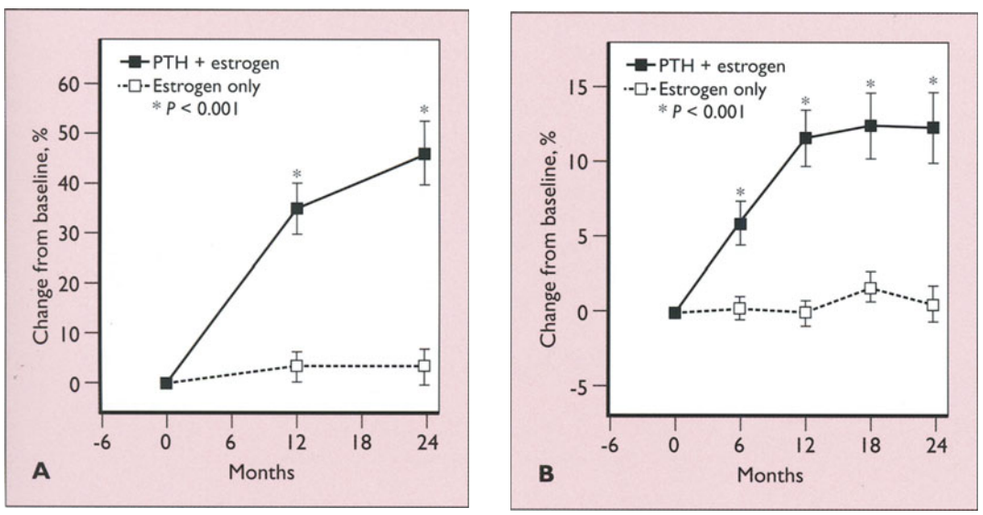



**FIGURE 12-24.** Parathyroid hormone (PTH) treatment in patients receiving glucocorticoids. In light of the reduction in bone formation that occurs in glucocorticoid-induced osteoporosis, and the positive effects of PTH therapy on bone formation and bone mass, therapy with PTH may be quite effective in patients receiving glucocorticoids. In fact, Lane *et al* [39] reported that postmenopausal women with osteoporosis who were receiving glucocorticoids (and were already on estrogen) responded to PTH therapy with a large increase in bone mineral density. The increase continued even after the PTH was discontinued. Although no large fracture prevention trials have been completed with PTH therapy in glucocorticoid-treated patients, these results are quite promising. **A,** Mean percent change (± SEM) from baseline of lumbar bone mineral density measured by QCT. **B,** Mean percent change measured by DXA.

**RECOMMENDED APPROACHES TO THE PREVENTION OF AND THERAPY FOR GLUCOCORTICOID-INDUCED OSTEOPOROSIS**

- Patient beginning therapy with glucocorticoid (prednisone equivalent of 5 mg/d) with plans for treatment duration of 3 months
  - Modify lifestyle risk factors for osteoporosis
  - Smoking cessation or avoidance
  - Reduction of alcohol consumption if excessive
  - Instruct in weight-bearing physical exercise
  - Initiate calcium supplementation
  - Initiate supplementation with vitamin D (plain or activated form)
  - Prescribe bisphosphonate (use with caution in premenopausal women)
- Patient receiving long-term glucocorticoid therapy (prednisone equivalent of 5 mg/d)
  - Modify lifestyle risk factors for osteoporosis
  - Smoking cessation or avoidance
  - Reduction of alcohol consumption if excessive
  - Instruct in weight-bearing physical exercise
  - Initiate calcium supplementation
  - Initiate supplementation with vitamin D (plain or activated form)
  - Prescribe treatment to replace gonadal sex hormones if deficient or otherwise clinically indicated
  - Measure BMD at lumbar spine and/or hip
  - If BMD is not normal (*ie*, T score below -1), then
    - Prescribe bisphosphonate (use with caution in premenopausal women)
    - Consider calcitonin as second-line agent if patient has contraindication to or does not tolerate bisphosphonate therapy
  - If BMD is normal, follow up and repeat BMD measurement either annually or biannually

**FIGURE 12-25.** American College of Rheumatology recommended approaches for the prevention of and therapy for glucocorticoid-induced osteoporosis. The American College of Rheumatology has reviewed the information available concerning glucocorticoid-induced osteoporosis and formulated a series of recommendations for its prevention and therapy [37]. They assume that calcium and vitamin D supplementation, physical activity, and addressing other risk factors for fracture form the basis of prevention. Moreover, the use of bone density measures can be instrumental in selecting patients for more aggressive diagnostic and therapeutic intervention. Finally, bisphosphonates can be very effective in preventing bone loss, or reversing loss, in glucocorticoid-treated patients. BMD—bone mineral density.

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# 13

# *Immobilization Osteoporosis*

*B. Jenny Kiratli*

Bone loss occurs with inactivity and immobilization. Just as bone mass increases during growth and development and with exercise attributable to increases in mechanical loading, bone mass decreases with reduced mechanical use. This response has been recognized for more than 50 years and has been evaluated in many clinical conditions. However, much remains unknown about underlying mechanisms, and there have been few successful demonstrations of countermeasures for prevention or treatment. Clinical immobilization includes a variety of situations, ranging from temporary recumbency during recovery from surgery, to permanent paralysis resulting from a traumatic spinal cord injury, and site-specific bone loss occurs relative to the magnitude of immobilization. Although osteopenia has been reported in diseases and conditions that cause temporary or partial immobilization, few detailed studies have been conducted and available information is fairly general. A larger body of literature concerns bone loss with complete paralysis due to spinal cord injury [1]. The concepts discussed here related to bone response to paralysis are expected to apply to other, less extensive immobilizing conditions, but with reduced magnitude.

Spinal cord injury is the most extreme case of clinical immobilization: Complete paralysis of particular body regions is frequently the outcome, and the observed osteopenia may be considered a worst-case scenario of skeletal response to reduced mechanical loading. Paralysis caused by spinal cord injury reflects the location and extent of neurologic damage. Injuries in the cervical region of the spinal cord result in tetraplegia because they affect both upper- and lower-extremity function. Injuries below this area cause paraplegia because the brachial plexus is preserved and only lower-extremity function is altered or eliminated. This simple distinction regarding motor function does not address the multitude of other organ and regulatory functions that are affected by the level of the injury. However, this chapter explores bone atrophy with regard to loss of motor function; thus, body and limb immobility are the primary focus of this discussion. Furthermore, injury to the spinal cord may include partial interruption of neural transmission; that is, some, but not all, neurons in the injured part of the cord are damaged. This results in "incomplete" paralysis and preservation of some amount of motor function relative to intact neurons. Thus, even spinal cord injury does not necessarily lead to complete cessation of mechanical loading.

Acute paralysis resulting from spinal cord injury is characterized by hypercalciuria and heterotopic ossification (the incidence rate was previously 25% but has recently been decreasing). Hypercalcemia is infrequent, except in younger patients. There is an immediate elevation of both bone formation and resorption activity, but a greater elevation of resorption, resulting in a net loss of bone. Most bone loss occurs in the first year after injury, and bone turnover stabilizes within 4 years after injury.

As with other conditions of bone loss, osteopenia, in itself, is not a problem until it contributes to elevated risk of fracture. Both the patterns and the treatment of fracture are unique in patients with spinal cord injury. The underlying risk factors and risk profiles may also differ from those of patients diagnosed with other forms of osteoporosis.

This chapter covers basic concepts regarding bone biomechanics with a focus on reduction of mechanical loading and the manner in which bone responds to alterations in its mechanical environment; clinical evidence of osteopenia resulting from disuse and immobilization with primary focus on spinal cord injury; relevant information about fractures in patients with spinal cord injury; and a theoretical framework for understanding bone loss and fracture risk with decreased mechanical loading.

# Bone Biomechanics

**TYPES OF MECHANICAL LOADING**

| External Loads on the Body | Internal Loads on Bone |
|---|---|
| Ground reaction forces/gravity | Compression |
| Body weight | Tension |
| Body segmental mass | Torsion |
| Muscle activity | Shear |
| Impact | |

**FIGURE 13-1.** Types of mechanical loading. During normal movement, the human skeleton is constantly subjected to external and internal loads, and these loads so strongly influence bone tissue that the tissue adapts structurally. Bone becomes deformed from bending, compression, and torsion loads. External loads can include ground reaction forces generated during walking, running, or climbing steps; compression and torsion imposed by the mass of body segments at rest and during movement; and forces generated by muscular contractions and impact loading (such as hitting a tennis ball or jumping). Internal compressive, tensile, torsional, and shear strains (deformation) are generated within the bone tissue as a result of these external loads. Strain direction, strain distribution, strain rate and frequency, and stimulus duration all are components of the mechanical control of bone response. Although cellular mechanisms are not yet thoroughly understood, a growing body of evidence identifies the physical, electrical, and endocrine factors involved in the translation of skeletal mechanical loading condition to cellular osteogenic response [2].

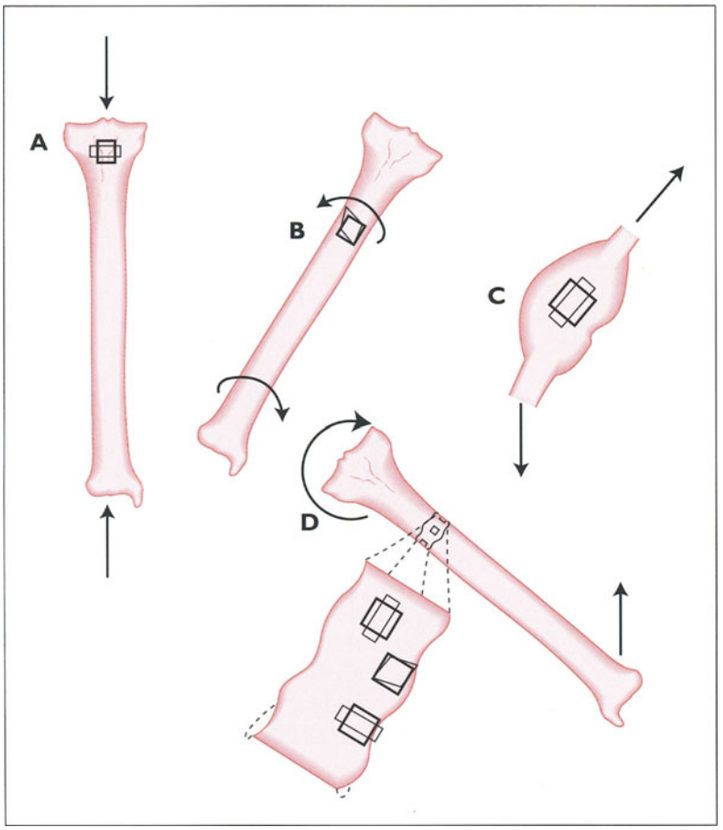


**FIGURE 13-2.** Bone deformation in response to loading. Bone deformation initiates the bone remodeling response. These diagrams show the internal strains generated within the bone by mechanical loading. The thick lines are the undistorted shapes, and the thin lines are the distorted ones. The deformations, much exaggerated, are compression (**A**); torsion, producing shear (**B**); tension, as in the patella (**C**); and bending (**D**). In *D*, the deformations are shown on a piece of bone unwrapped from the whole bone. The lower part shows tension; the middle shear; and the top compression. (*Adapted from* Currey [3]; with permission.)

**EXAMPLES OF BONE ADAPTATION TO MECHANICAL LOADING**

| Influence | Effect |
|---|---|
| Growth and development | Increased bone mass |
| Exercise and increased physical activity | Increased bone mass |
| Disuse or immobilization | Decreased bone mass |

**FIGURE 13-3.** Examples of bone adaptation to mechanical loading. Much clinical and experimental evidence indicates that bone tissue adapts to alterations in mechanical use. Bone accretion occurs during adolescence as a result of normal growth and development. Evidence that body mass predicts bone mass increment during growth supports the expectation that mechanical loading is an important factor [4]. In other words, the loads imposed on the developing child by his or her body weight influence skeletal regulation. Physical activity, especially resistance exercise, leads to increased bone formation in the young adult. Reduction in physical activity leads to reduction in bone in the older adult; increase in bone mass has been demonstrated in older adults engaging in an impact loading exercise regimen [5]. Decreased loading in experimental or therapeutic recumbency (*ie*, bedrest) or in diseases and conditions of immobilization causes decreased bone mass.

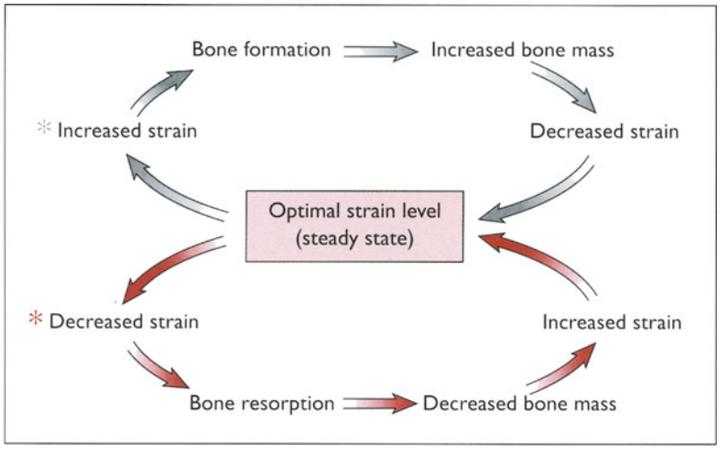


**FIGURE 13-4.** Regulation of bone mass. Bone accommodates to a customary mechanical loading environment; changes in this environment are reflected by changes in tissue-level stimulus, which results in changes in bone mass. Increased external loading leads to increased tissue-level strain, and bone formation is initiated to regain the customary strain environment. Increasing bone mass reduces the strain level, and a feedback loop is established until a new equilibrium is achieved. Bone responds to dynamic loading, rather than static loading, and only a short duration of loading, if the magnitude is sufficient, is necessary to initiate bone adaptation [6]. Conversely, reduction in external loads causes initiation of bone resorption and decreased bone mass in order to maintain customary strain level. Several theories have been proposed regarding the regulatory mechanisms of this adaptive effect [7].

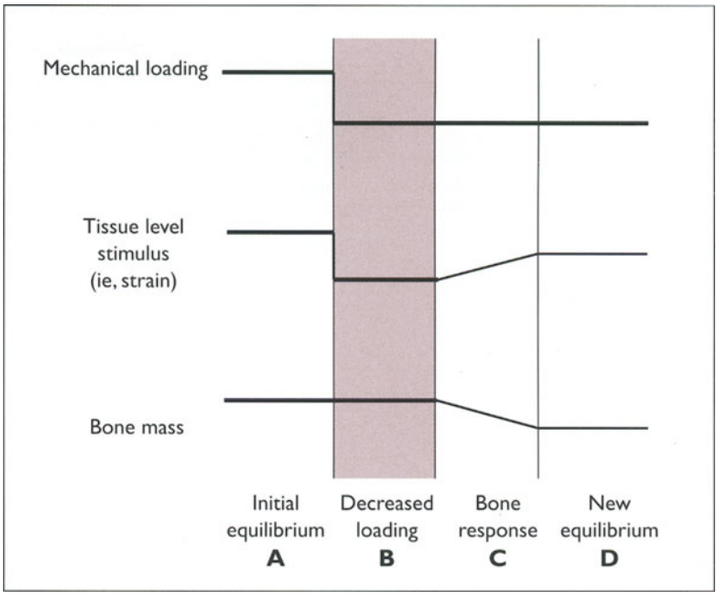


**FIGURE 13-5.** Adaptation of bone mass to immobilization. **A,** An equilibrium exists within bone in relation to its mechanical environment. **B,** If habitual mechanical use declines, tissue-level strain declines. **C,** Bone tissue responds by reducing mass; this allows the strain level to return to normal or to an optimal level. **D,** A new equilibrium is established in relation to the now habitual condition of decreased loading.

**EFFECTS OF MECHANICAL USAGE ON MODELING AND REMODELING**

| Effects on Skeletal Envelopes | Modeling | Remodeling |
|---|---|---|
| *Increased Strain* | *Activated* | *Inhibited* |
| Periosteal | Apposition | Expansion ?? |
| Endosteal | Loss retarded | Loss retarded |
| Trabecular | Loss retarded | Loss retarded |
| Intracortical | No effect | Activation retarded; increased mass |
| *Decreased Strain* | *Inhibited* | *Activated* |
| Periosteal | Apposition retarded ?? | Apposition retarded ?? |
| Endosteal | Loss accelerated | Loss accelerated |
| Trabecular | Loss accelerated | Loss accelerated |
| Intracortical | No effect | Activation stimulated; loss of bone mass |

**FIGURE 13-6.** Differential response by bone tissue. Bone adapts by different mechanisms in the bone envelopes in response to alteration in the local mechanical environment. Mechanical loading includes a complex set of stimuli that are not uniform throughout the bone. This table summarizes expected responses in periosteal, endosteal, trabecular, and intracortical bone envelopes caused by elevated and decreased loading, in circumstances of both modeling (accretion of new bone) and remodeling (reorganization of existing bone). (*Adapted from* Martin and Burr [7]; with permission.)

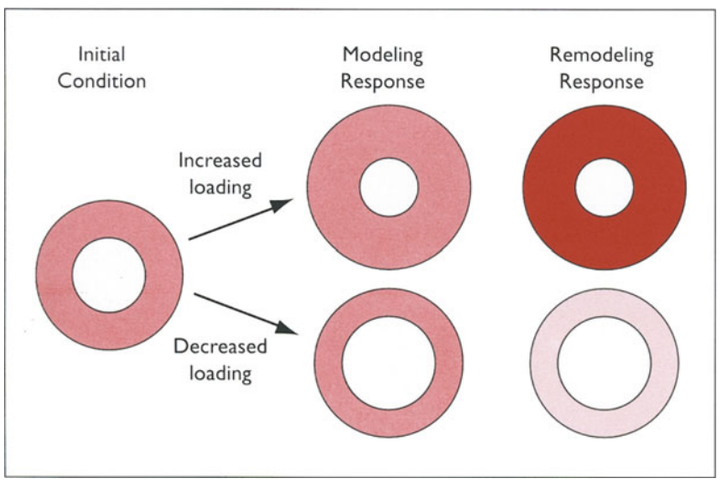


**FIGURE 13-7.** Modeling and remodeling responses to the increased and decreased mechanical loading described in Fig. 13-6. Periosteal expansion and increased cortical thickness occur with increased loading, and intracortical density may increase (indicated by darker shading) with remodeling. Cortical thinning is found with decreased mechanical loading, and intracortical density may be reduced with remodeling.

# Clinical Evidence

**MODELS OF IMMOBILIZATION**

- Animal models
  - Tendon resection: rabbit
  - Hindlimb suspension: rat
  - Intact, isolated wing: turkey
  - Spinal cord transection: cats
  - Limb casting: dogs
  - Body cast immobilized: monkey
- Spaceflight
  - Astronauts
- Bedrest
  - Healthy volunteers

**FIGURE 13-8.** Models of immobilization. Evidence of bone atrophy in circumstances of experimental or situational disuse or immobilization is available from animal studies and studies of hypogravity and voluntary bedrest in humans. Various techniques have been used to simulate disuse and immobilization in animal studies. This table presents the more frequently used animal models, including examples of both irreversible and reversible immobilization. Data are available on histologic responses and mechanical properties of atrophied bone, as well as quantification of muscle atrophy and its correlation with bone response. Many of these studies have also yielded specific information about the amount and type of loading stimulus necessary to maintain normal bone homeostasis. In the 1970s, NASA began to investigate the effects of weightlessness on the skeleton and studied astronauts participating in space flight as well as earthbound volunteers put to extended bedrest. The findings from these studies are applicable to understanding clinical conditions of immobilization. These studies have also investigated potential countermeasures to prevent bone loss, including pharmacologic therapy (bisphosphonates) and physical means (eg, recumbent cycling and impact or compressive loads applied to the feet). Currently, astronauts engage in resistance treadmill exercise during space flight, in part to prevent bone atrophy. In both animal and human models, much of the bone loss appears to be reversible with return to normal mechanical loading, although evidence in one study of astronauts indicates a long-term bone mass decrement in later years following spaceflight.

**CLINICAL EXAMPLES OF IMMOBILIZATION**

- Temporary immobilization
  - Therapeutic bedrest (eg, prolapsed disc)
  - Injury
- Paretic disorders
  - Poliomyelitis
  - Cerebral palsy
  - Multiple sclerosis
  - Stroke
- Paralysis
  - Spinal cord injury
- Other conditions
  - Amputation
  - Total joint replacement
  - Regional disorder (eg, frozen shoulder)

**FIGURE 13-9.** Clinical examples of immobilization. There are numerous occurrences of disuse and immobilization in clinical circumstances. Physical activity and thus mechanical loading may be temporarily reduced in cases of injury or therapeutic bedrest, and long-standing reduction in habitual physical activity is concomitant with aging or general health decline in many individuals. Overall or specific weakness (paresis) and regional paralysis are found with disorders that may occur primarily in childhood, such as spina bifida, cerebral palsy, and poliomyelitis; with some degenerative diseases in adulthood, such as multiple sclerosis; and with stroke. Complete or partial paralysis results from spinal cord injury. Normal mechanical loading is also decreased in various other conditions, such as limb amputation, where muscle attachments are severed and muscles proximal to the amputation are immobilized; total joint replacement, in which stress-shielding occurs as the normal loads are essentially diverted from the bone to the prosthesis; and localized joint immobility. In all these conditions, localized bone loss is observed concurrently with reduction in mechanical use. In hemiparetic conditions, such as stroke, compensatory increase in use (and therefore increased bone mass) may occur on the unaffected side that is overloaded during ambulation or otherwise used more frequently in place of the affected side.

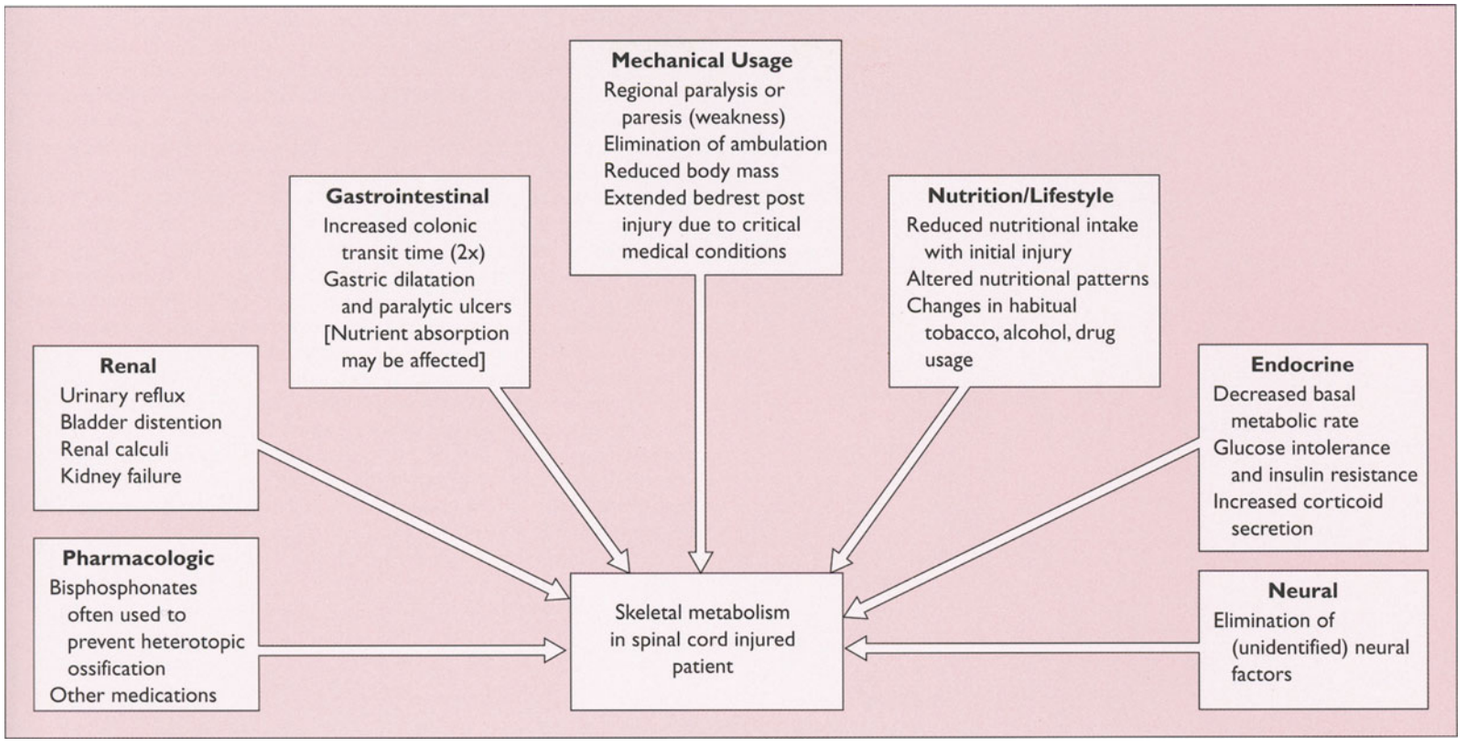


**FIGURE 13-10.** Physiologic factors that can influence bone response following acute spinal cord injury resulting in paralysis. Myriad medical and lifestyle changes occur with spinal cord injury, and changes in these factors can contribute to bone response. Although it is commonly thought that motor paralysis is the predominant factor underlying bone loss after paralysis (hence the common term "disuse osteoporosis"), other, as yet unidentified neural factors may also contribute (an alternative term is "neurogenic bone loss," which is more open-ended). In addition to the regional paralysis and resultant loss of ambulatory ability, there may be concurrent medical conditions, such as traumatic bone fractures, head injury, or other critical injuries that necessitate extended bedrest. As these medical conditions resolve, the patient will be encouraged to sit and move as much as he or she is able, and wheelchair mobility will be initiated. Muscle mass is rapidly lost following acute spinal cord injury because of both reduced use and denervation. The reduction in muscle mass and activity removes a primary factor of bone maintenance (mechanical loading). Patients also frequently experience great weight loss in the acute stage after a spinal cord injury. Nonmechanical factors that may influence bone response include endocrine, gastrointestinal, renal, and nutritional changes, changes in substance use (*ie*, tobacco, alcohol, drugs), and prescribed medications. No specific data on the effects of these changes on bone are available, but they should not be forgotten as potential factors.

**MARKERS OF BONE TURNOVER IN ACUTE AND CHRONIC SPINAL CORD INJURY**

| Bone Metabolism | Acute Response | Chronic Response |
|---|---|---|
| Formation markers: | | |
| Osteocalcin | Elevated | Normal |
| C terminus peptide, type I procollagen | Elevated | ? |
| Resorption markers | | |
| Hydroxyproline/creatinine ratio (urinary) | Elevated | Normal |
| Pyridinolines | Elevated | ? |
| C-terminus telopeptide, type I procollagen | Elevated | ? |
| Turnover markers | | |
| Serum ionized calcium | Normal | Normal |
| Calcium/creatinine ratio (urinary) | Elevated | Normal |
| Calcitonin | Elevated | Elevated/normal |
| Parathyroid hormone | Decreased | Decreased |
| 25-Hydroxycholecalciferol (vitamin D) | Decreased | Decreased |

**FIGURE 13-11.** Markers of bone turnover in acute and chronic spinal cord injury. Much of the early literature on bone loss with immobilization (1950s to 1970s, before the advent of densitometry) described effects of paralysis, specifically from poliomyelitis and spinal cord injury, on nonspecific markers of bone metabolism, such as alkaline phosphatase and hydroxyproline. Recent work with more specific markers has borne out the findings of these early researchers [8–11]. Immediately after injury, markers of both bone formation and bone resorption increase, with greater and more sustained increases in resorption markers. Thus, the initial bone remodeling response appears to represent an uncoupling of the osteoblast–osteoclast cellular actions that normally maintain a balance of bone formation and resorption. The result is a net loss of bone during this period. Hormone and metabolite levels of resorption markers remain elevated for up to 8 months and then return to normal or near-normal levels. By 12 months after injury, most markers are within the normal range and there is little evidence of abnormal bone metabolism in patients with chronic spinal cord injury. However, several recent studies indicate persistent vitamin D deficiency and parathyroid hormone depression [12–14]. Relatively few studies on this topic have been conducted, and specific results of these existing studies are somewhat inconsistent. Furthermore, not all patients conform to group findings; these disparate results may be attributable to underlying disease or other conditions. Finally, data are not yet available for some of the newer markers of bone metabolism for patients with long-standing spinal cord injury (these are indicated by "?" in the table).

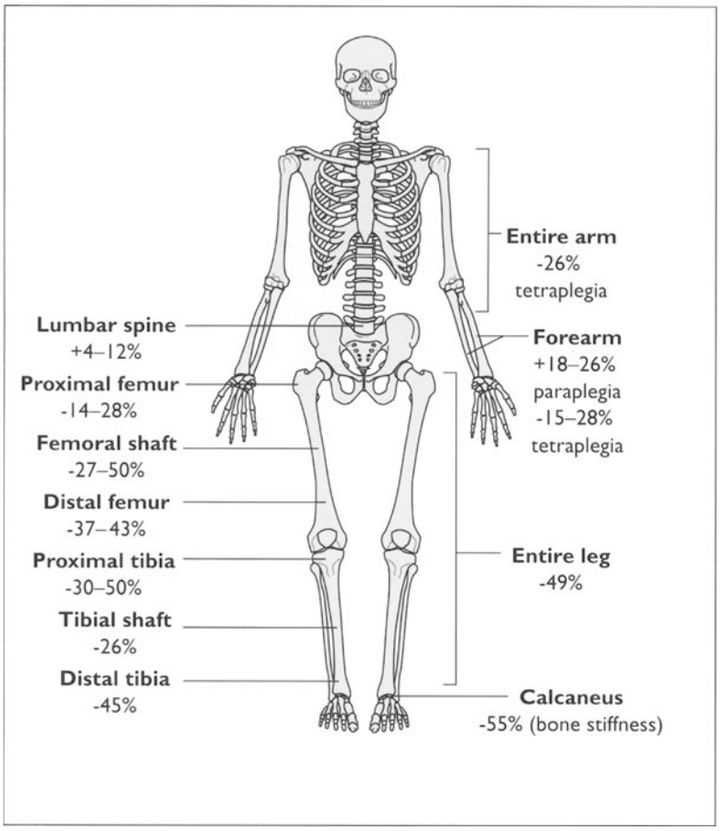


**FIGURE 13-12.** Regional bone loss after spinal cord injury. Local osteopenia is observed in relation to changes of mechanical loading. That is, bone loss occurs only in skeletal regions below the level of the lesion where motor function is reduced. Data are available from many studies; these results are summarized in the figure [17–35]. Total leg bone mass is reduced by approximately 50%, with regional changes as shown in the figure. There appears to be greater loss in the more distal segments and in the regions that consist primarily of cancellous bone. Equivalent bone decrement occurs in the lower limbs of both paraplegic and tetraplegic individuals; this is not surprising because the mechanical environment (*eg*, motor paralysis and absence of standing) of the lower extremity is essentially the same for both patient populations. Upper-extremity bone loss occurs with tetraplegia, but bone mass is commonly increased with paraplegia; these findings correspond with decreases and increases in upper-extremity function in tetraplegia and paraplegia, respectively. In both paraplegic and tetraplegic patients, lumbar spine bone mass increases. While the level of the neurologic lesion determines which skeletal regions are affected (*ie*, regions distal to the injury), the severity of the injury, or "completeness," also contributes to the magnitude of the effect; this might explain some of the variability in observed bone response in studies that have not controlled for completeness. With an incomplete spinal cord injury, voluntary motor function may be preserved to varying degrees below the level of the lesion. Thus, some amount of mechanical loading is preserved, and the bone response is less [27].

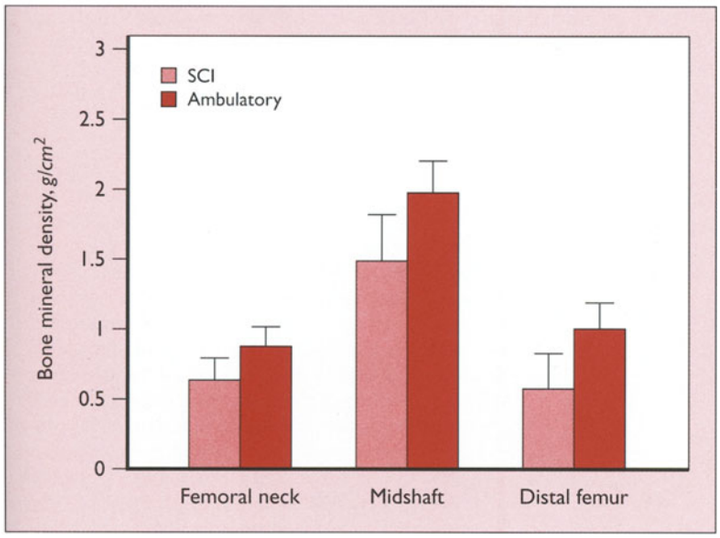


**FIGURE 13-13.** Bone mineral density in three femoral regions—comparisons between patients with spinal cord injury (SCI) and ambulatory controls. Bone mineral density ($g/cm^2$) summary values are reported for 241 men with chronic SCI compared with 37 male controls. Results for ambulatory controls are presented in the dark bars, and those for subjects with SCI in the light bars. Significant decreases are found in patients with SCI at each of the three measured regions in the femur [32].

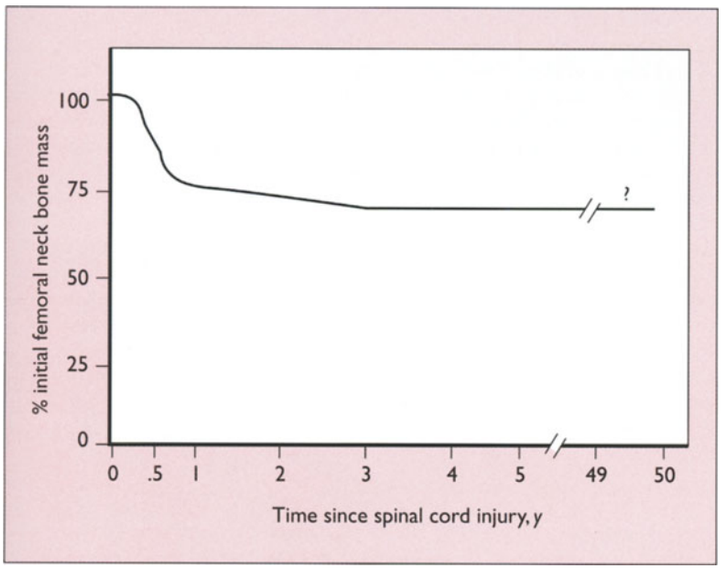


**FIGURE 13-14.** Femoral neck bone response with acute and chronic spinal cord injury. Few data are available on bone mass for the first few days after spinal cord injury primarily because of logistic problems with making these measurements. However, even though the metabolic changes begin immediately, little observable change in bone mass would be expected because of the time delay of bone remodeling (*ie*, 4 to 6 weeks for bone mass change). This schematic, based on available data, shows bone response in the femoral neck. Individual responses vary greatly, and measurement intervals are often variable for individual patients and across studies. Reduction in femoral neck bone mineral density is greater in the early months after acute immobilization (approximately 2% per month for the first 5 to 7 months) than in the later months (less than 1% per month for the remainder of the year). The average loss over the first year is approximately 20%. Few data are available for the loss rate within the next few years after injury, but some continuing loss seems to occur with average total loss up to 30%. Bone mass appears to stabilize by the fourth year, with little evidence of later loss even after many decades of paralysis. Bone response in the leg does not differ between tetraplegic and paraplegic patients. No evidence suggests an independent age effect on bone response, and there is little evidence of increasing bone loss with greater duration of injury (although some reports indicate such an effect [36]).

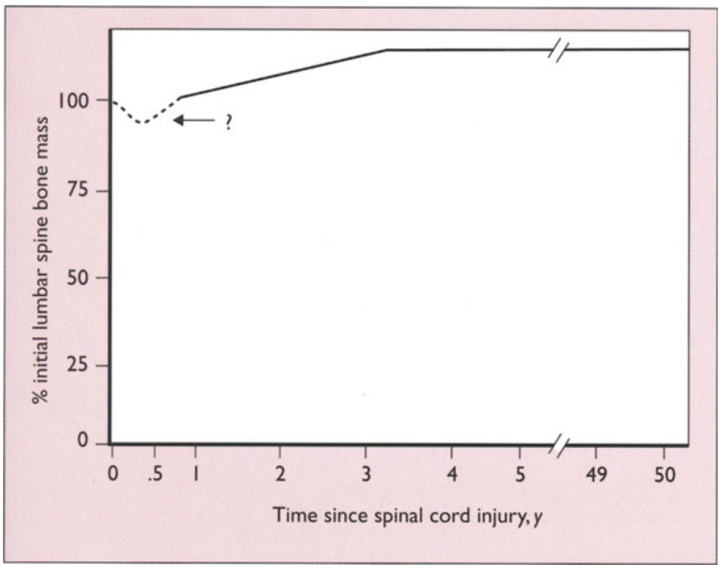


**FIGURE 13-15.** Lumbar spine bone response with acute and chronic spinal cord injury. Bone response at the lumbar spine shows a different pattern from that seen at the hip. Essentially no reduction attributable to paralysis occurs in this region. However, an initial but reversible decline may occur in patients subjected to extreme recumbency because of additional medical complications. In fact, some evidence suggests a slight increase in bone mineral density of the lumbar spine in chronic paralysis (up to 12% above normative values). As with bone mineral density of the femoral neck, duration of injury has no effect, and there is no difference between individuals with tetraplegia and those with paraplegia. The commonly accepted explanation for maintenance of lumbar spine bone mass is that patients with spinal cord injury carry their body weight during daily activities via a sitting position; thus, normal loading patterns may not be substantially disrupted and may be similar to those of ambulatory individuals. The observed increase may result from abnormal loading patterns imposed with wheelchair posture and altered mechanical loading due to reduced or absent back musculature.

**THERAPIES FOR PREVENTING BONE LOSS IN SPINAL CORD—INJURED PATIENTS**

| Therapy | Effect on Bone Mass |
|---|---|
| Upright loading (standing) | No evidence |
| Electrical stimulation exercise | Equivocal evidence of reduction in bone loss |
| Pharmacologic | Equivocal evidence of reduction in bone loss |

**FIGURE 13-16.** Therapies for preventing bone loss in patients with spinal cord injury. For many decades, clinicians and researchers have sought effective countermeasures for the bone loss associated with disuse and immobilization. Few reports in the literature describe successful treatments, however. Much attention has focused on physical countermeasures based on the expectation that the primary cause of bone loss is elimination of mechanical loading; thus, replacement or simulation of mechanical loading should reverse bone loss. Upright standing in a standing frame or with braces has not been shown to reduce osteopenia. However, standing protocols have involved relatively brief frequency of stimulus (1 hour per day, 3 times per week) and include static loading only; dynamic loading, which causes bone deformation, is required to elicit a bone response. Electrical stimulation of leg musculature during cycling exercise has recently been shown to positively affect bone mass [37], but many prior studies have not shown such an effect. Pharmacologic treatments (including calcitonin, etidronate, clodronate, toludronate, and pamidronate) have also been attempted, with mostly negative results; some evidence indicates a positive effect on bone turnover assessed by biopsy and with metabolic markers [38–42], but few data on bone mass change have been published. Bisphosphonate treatment (primarily etidronate) has been found to be successful in preventing heterotopic ossification [43]. Currently, clinical trials are underway to determine the efficacy and effectiveness of alendronate in preventing early bone loss and/or reversing long-standing osteopenia; the results are not yet available, but preliminary reports are encouraging [44].

**BONE RESPONSE FOLLOWING STROKE**

Decrement in BMD on paretic side compared with unaffected side
- Arm, 8%–12%
- Leg, 3%–5%

Bone loss is positively correlated with duration of stroke, negatively with motor function; this effect is more apparent in the arms than the legs

Metabolic responses include decreased vitamin D concentrations ($1,25\text{-}[OH]_2D$ and 25-OH), serum parathyroid hormone (PTH), and bone GLA protein (a marker of bone formation)

Recovery of ambulation ameliorates bone loss in the lower extremity

**FIGURE 13-17.** Bone response following stroke. One other patient population has generated a moderate clinical literature on immobilization osteoporosis. Regional bone loss occurs in patients with unilateral stroke (hemiplegia) in the upper and lower extremity on the affected/paretic side compared with the unaffected side. Bone metabolism is altered, favoring bone resorption, and vitamin D deficiency is commonly present, especially after acute stroke [45, 46]. Reduction in bone mass is more pronounced in the upper than the lower extremity and is associated with level of disuse and amount of residual function [47–51]. Few studies have quantified fracture prevalence in this population, and only equivocal evidence exists to support this outcome [52–54]. Returning to weightbearing status by relearning to walk reduces bone loss in the affected lower extremity [55]. Thus, the association between mechanical loading and bone response is demonstrated clinically in these patients; however, relatively few studies have been conducted in this population and much remains undiscovered about the clinical consequences of and indications for treatment. BMD—bone mineral density.

# Long Bone Fractures after Spinal Cord Injury

**SYMPTOMS AND INDICATIONS OF FRACTURE IN THE SPINAL CORD–INJURED PATIENT**

Swelling and erythema

Increased autonomic dysreflexia

Increased spasticity

Patient experienced a sound ("pop" or "crack") that indicated fracture

Limb deformity

**FIGURE 13-18.** Symptoms of fracture in patients with spinal cord injury. Fractures frequently occur in such patients without evidence of trauma and often go undiagnosed acutely because of absent sensation and lack of a traumatic event. In some instances, the patient is aware of a sound (loud crack or pop) when the limb fractures (*eg*, while performing a leg-stretching exercise or during dressing). Common symptoms include local swelling and redness, increased spasticity or autonomic dysreflexia, and, occasionally, deformity. Essentially, the untransmitted pain of the fracture acts as an internal noxious stimulus that heightens the nervous system responses (spasticity and potentially life-threatening autonomic dysreflexia). In the absence of obvious causes of autonomic dysreflexia, the examining physician should evaluate the possibility of a pathologic or unnoticed bone fracture in these patients.

**LOCATION AND FREQUENCY OF LONG BONE FRACTURES IN SPINAL CORD–INJURED PATIENTS**

| Skeletal Region | Prevalence (Published Data) | Prevalence (Current Study) |
|---|---|---|
| Femoral neck | 12.5% | 13% - all proximal |
| Inter/subtrochanteric | 4.9% | |
| Femoral shaft | 12.8% | 19% |
| Supracondylar (femoral) | 29.6% | 22% |
| Tibial plateau | 2.3% | 19% - all proximal |
| Tibial proximal shaft | 6.6% | |
| Tibial midshaft | 8.6% | 13% |
| Tibia distal shaft | 13.2% | 13% |
| Other leg (not specified) | 10.5% | |

**FIGURE 13-19.** Location and frequency of long bone fractures. Most long bone fractures that occur after spinal cord injury are in the lower extremity. This is consistent with the expectation of specific bone loss with regional paralysis or paresis. The morphologic types and locations of these fractures are distinct from those seen in other osteoporotic populations. The predominant fracture types and sites are spiral fracture of the femoral shaft; displaced, bending fractures of the femoral (distal) condylar region; and simple fractures of the proximal tibia. Estimates of the proportion of fracture types are provided from the literature [56–60] and a recent study [Kiratli BJ, Unpublished data]. The overall prevalence of long bone fractures is estimated at approximately 6%, but this may be an under-representation because of data collection methods. The current rate may be much closer to 20% [61].

**CHARACTERISTICS OF SPINAL CORD–INJURED PATIENTS WHO SUSTAIN LONG BONE FRACTURES**

More common in paraplegia
More common with flaccid paralysis
More common with complete paralysis
Average duration of spinal cord injury: ≈11–15 y
High frequency of multiple fractures

**FIGURE 13-20.** Characteristics of patients with spinal cord injury who sustain long bone fractures. The proportion of fractures is higher in paraplegic than in tetraplegic patients; flaccidity and complete injury are also common patient characteristics. Although these fractures can occur at any time after spinal cord injury, the median time after injury is between 11 and 15 years. Patients frequently sustain multiple fractures at different times (two to three distinct fractures is not an uncommon occurrence, and some patients have more than five), although this does not include refracture of previous fracture sites.

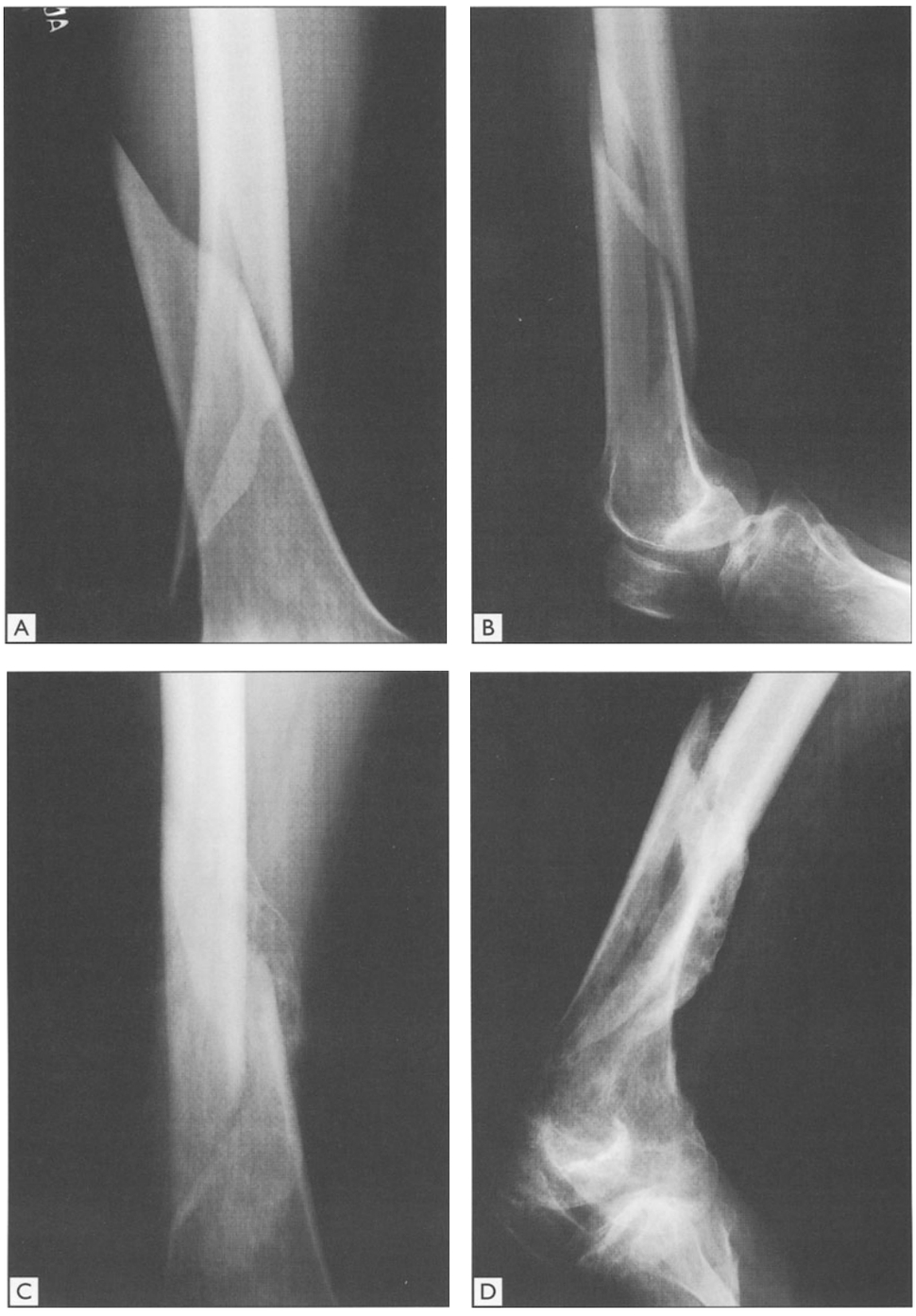


**FIGURE 13-21.** Spiral fracture of the femoral shaft. One of the most common and spectacular fractures in patients with spinal cord injury is the spiral fracture of the femoral shaft. This figure shows the anteroposterior (**A,C**) and lateral (**B,D**) views of an initial (**A** and **B**) and healed (**C** and **D**) femoral fracture in a 47-year-old, complete tetraplegic man whose spinal cord (C7) injury occurred 12 years before the fracture. Although neither internal nor external fixation was performed, these fractures tend to heal solidly, albeit sometimes in malalignment. A common mode of this type of fracture is catching the foot in the wheelchair during a transfer.

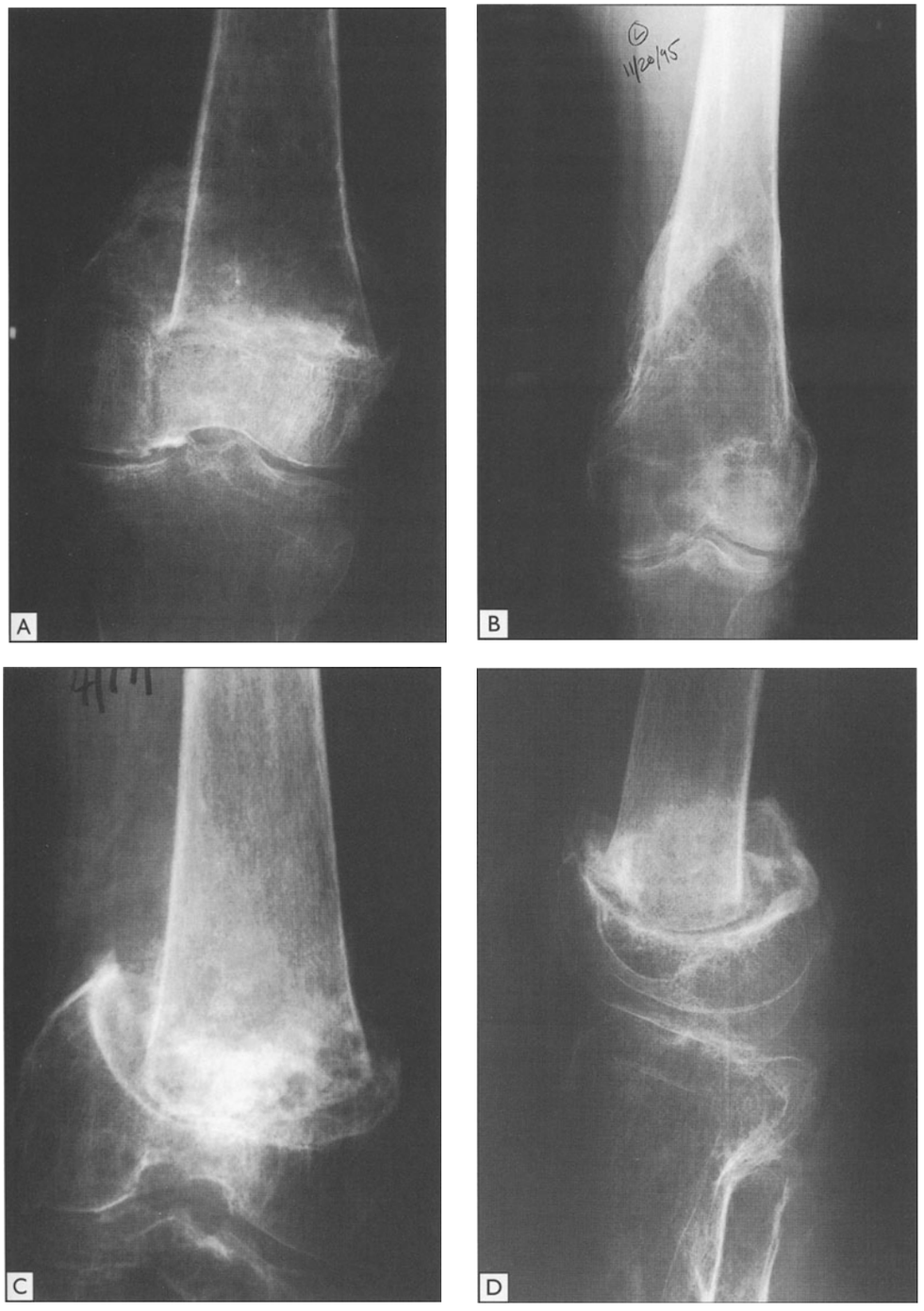


**FIGURE 13-22.** Displaced fracture of the distal femur. Another common fracture occurs in the highly cancellous region of the distal femur. Treatment is conservative, and orthopedic fixation is not usually offered. This type of fracture is somewhat more likely to result in nonunion or pseudarthrosis, or it may involve excessive bone formation within the distal joint. Several healing responses after this type of fracture are shown. Successful healing is shown for (**A**) an 80-year-old complete paraplegic man whose spinal cord injury (T12) occurred 54 years before the fracture and (**B**) a 37-year-old complete tetraplegic man whose spinal cord injury (C6) occurred 11 years before the fracture. A nonunion is shown in anteroposterior (**C**) and lateral (**D**) views in a 76-year-old complete paraplegic man whose spinal cord injury (T4 and T5) occurred 19 years before the fracture. The more distal fractures seem to have worse healing outcomes. In some cases, joint fusion occurs as a sequela of extensive heterotopic bone formation that extends into the femorotibial joint space. Resection may be offered to patients with this condition to regain joint mobility, but excessive bone formation may recur after resection surgery. Furthermore, bone resection in this area may be difficult because of the potential for damage to the neurovascular bundle encased in bony tissue. The clinical decision should include consideration of the effect of the immobile joint on activities of daily living, such as sitting, transferring, and wheelchair mobility. A common mode of this type of fracture is falling from the wheelchair to the knees.

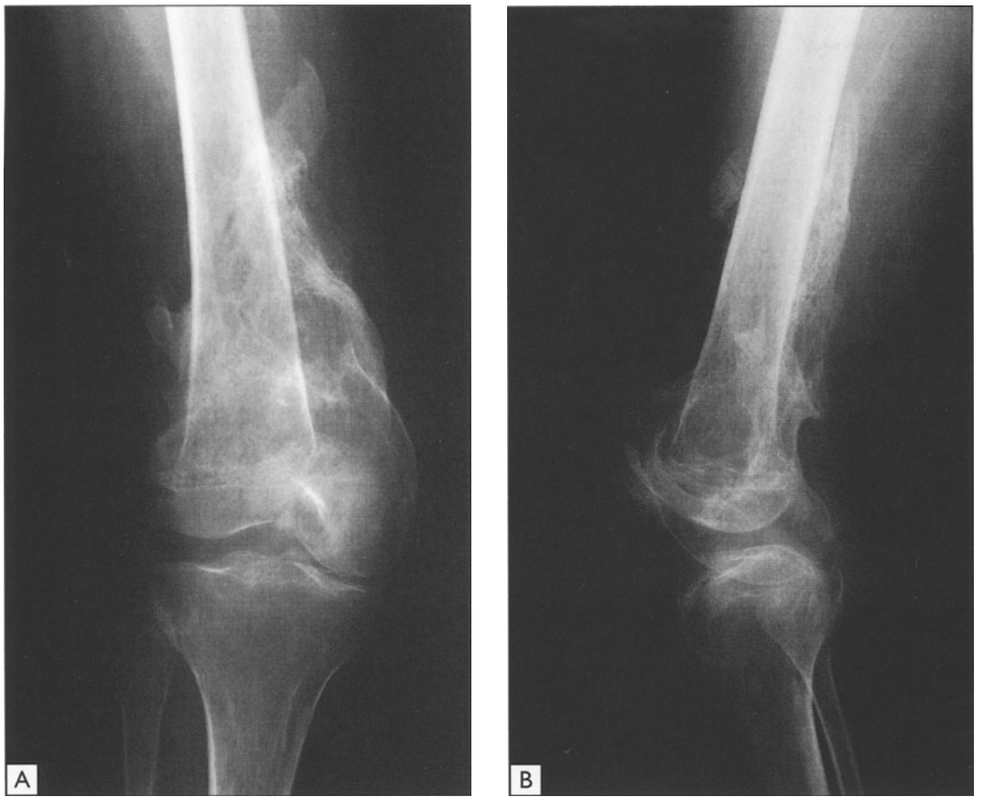


**FIGURE 13-23.** Exuberant callus formation. One of the distinctive features of long bone fracture healing with spinal cord injury is the formation of "exuberant" callus. This type of callus has a cloudy, disorganized appearance with no alignment along stress lines. Although typical in spinal cord injury, it is not characteristic of all fractures, and callus formation often appears normal in these patients. Furthermore, the formation of exuberant callus does not seem to interfere with the healing process. The patient shown here is a 32-year-old complete paraplegic man whose spinal cord injury (T12) occurred 8 years before the fracture. Anteroposterior (**A**) and lateral (**B**) views are shown.

**CAUSES OF FRACTURES IN SPINAL CORD–INJURED PATIENTS**

- Nontraumatic
  - Fall from wheelchair
    - During transfer activity
    - Activity of daily living
    - Range of motion exercise
  - Unknown
- Traumatic
  - Fall, other than from wheelchair
  - Motor vehicle accident
  - Other accident

**FIGURE 13-24.** Common causes of fractures. Most fractures occur with minimal or no trauma. In some cases, the cause is unknown because of absent sensation. With improved understanding of risky activities, fracture prevention regimens might be implemented. A significant number of fractures also result from traumatic causes. Although these fractures cannot be predicted on the basis of bone mass testing, cannot be prevented, and may occur in patients with adequate bone mass, precautions relative to skin fragility and infection must be maintained during treatment decision making.

**TREATMENT REGIMEN FOR LONG BONE FRACTURES IN SPINAL CORD–INJURED PATIENTS**

| Treatment Approach | Indication | Reason |
|---|---|---|
| Conservative treatment soft (pillow) splint and external brace | Commonly used | Safe, effective in promoting healing in most cases |
| Cast fixation | Contraindicated; less risk with bivalve cast | Skin fragility/risk of skin breakdown. Bivalve cast allows skin checks |
| Surgical fixation: prosthesis, plates, and rods | Contraindicated | Risk of infection, poor bone stock, skin fragility |

**FIGURE 13-25.** Treatment regimen. Although no consensus papers in the orthopedic literature concern optimal fracture management in patients with spinal cord injury, conservative, nonoperative treatments (such as pillow splinting or external bracing) are generally recommended; casts are used only if they are well padded and can be frequently removed for skin inspection. Surgical interventions (open reduction internal fixation) are generally contraindicated because of preexisting osteopenia, skin fragility, and heightened risk of further complications, including infection, continuous drainage, edema, hematoma, secondary hemorrhage, and refracture. Nonetheless, there are reports of successful surgical intervention in this patient population. Prolonged immobilization to achieve optimal healing has additional associated risks, such as joint contractures, postural deformities, general loss of cardiovascular fitness, and possible increase in bone turnover leading to accentuated osteopenia. The patient's prefracture functional abilities should be assessed, and treatment should be directed toward maximizing return to equivalent function. Treatment regimens vary, however, and are based mostly on the experience of the treating physicians in the absence of consensus protocols.

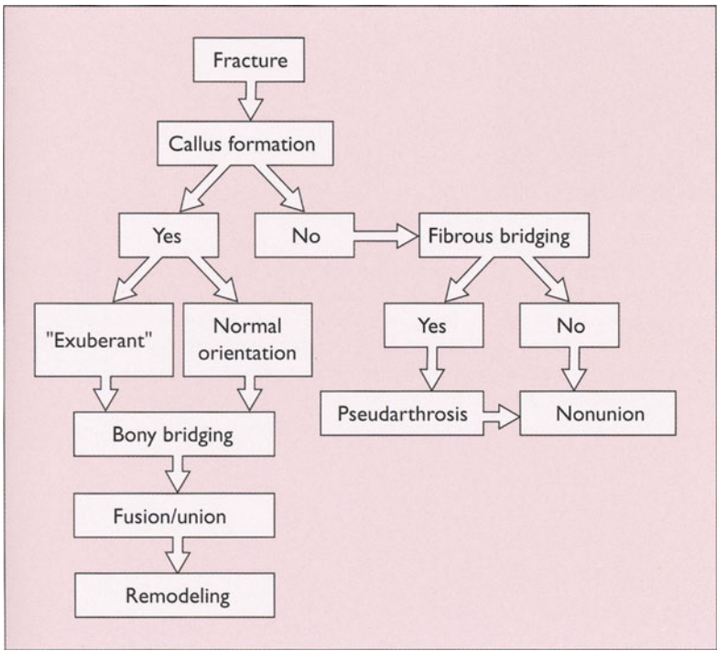


**FIGURE 13-26.** Healing response. Healing responses also vary. Adequate healing (bony union) occurs in most patients, although complications may occur; some patients, in contrast, do not form callus and tend not to heal fully (malunion or nonunion). Acute complications of fractures include hemorrhage and autonomic dysreflexia, and secondary complications such as infection and heterotopic bone formation may follow. Without proper management, outcomes can include spontaneous arthrodesis and loss of joint motion; malalignment resulting in functional deformity; and nonunion, which may develop into a pseudarthrosis. Unfused fractures can produce pain in patients with intact sensation and can interfere in activities of daily living because of abnormal limb mobility or stability. In a recent large epidemiologic study of fracture prevalence, healing was found to be rapid in most cases, with callus formation along stress lines and a high proportion of successful healing. Although malalignment was common, nonunion was relatively rare [Kiratli, Unpublished data]. Little is known about the reasons for different healing responses, nor about how often fractures might heal spontaneously in satisfactory positions without intervention. Orthopedic treatment decisions are influenced by fracture location and structure, the medical and physical status of the patient, and, primarily, the treating physician's experience with this population.

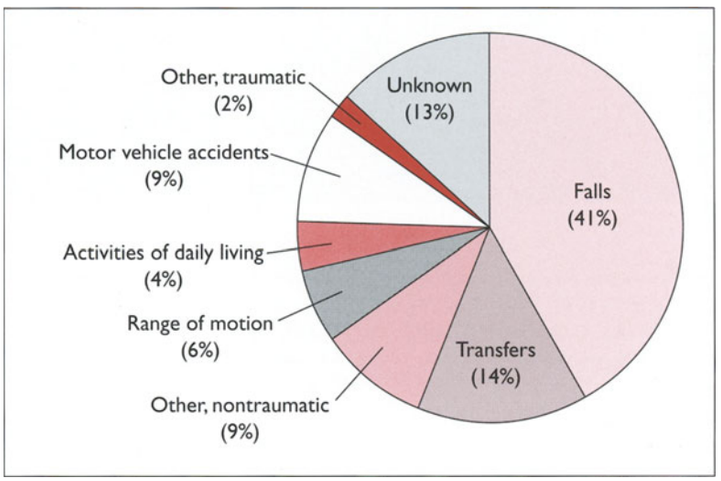


**FIGURE 13-27.** Fracture etiology of the lower extremity. The most common cause of fracture in the spinal cord–injured population is falls (41%), excluding falls during transfers. Lower-extremity fractures also commonly occur during transfers (14%) and while performing normal daily activities or exercises (10%). A relatively small proportion of fractures result from trauma. Programs aimed at fracture prevention should highlight the risks for this patient population of fracture occurrence during normal daily activities and emphasize how safe wheelchair mobility and transfers as well as added attention to body position can prevent the majority of these fractures [Kiratli, Unpublished data].

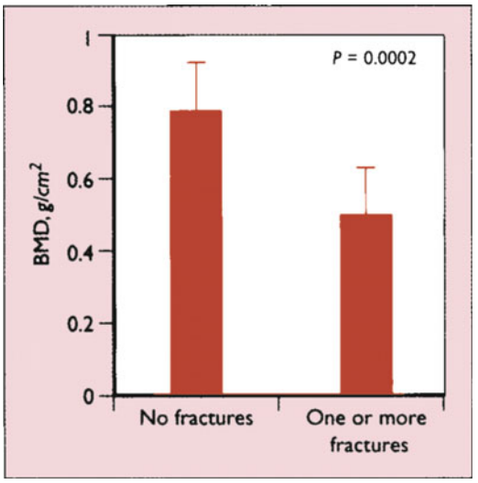


**FIGURE 13-28.** Bone mass and fracture history in patients with spinal cord injury. In a cross-sectional study, mean bone mass of the proximal femur was significantly decreased in patients with spinal cord injury who had a history of fracture (*dark shading*) compared with those who had no history of fracture (*light shading*) [62]. The sample consisted of 14 men with spinal cord injury who had sustained one or more fractures compared with 27 men with spinal cord injury who were fracture free. The cohort with positive fracture history had a longer duration of injury and was slightly older, but these variables did not contribute to fracture prediction in a multivariate analysis model. BMD—bone mineral density.

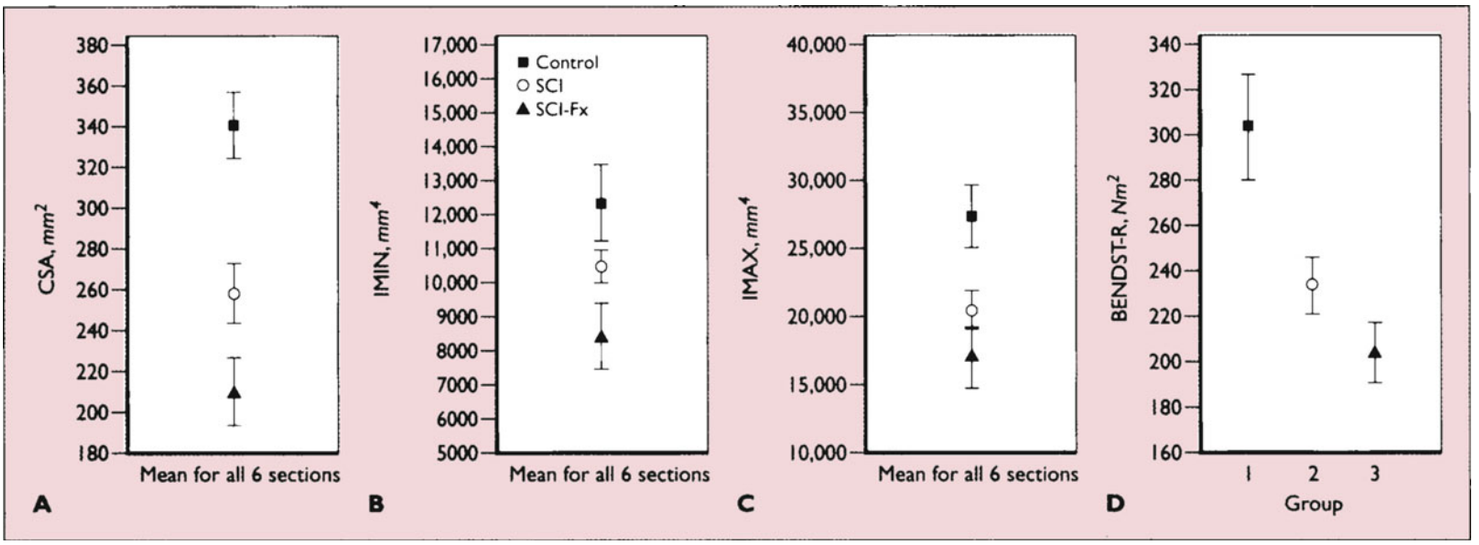


**FIGURE 13-29.** Bone geometric properties and fracture history in patients with spinal cord injury. Bone geometric indices determined by computed tomography on the tibial midshaft differ in patients with spinal cord injury who have and have not sustained lower-extremity fractures. Ten subjects were measured in each group. Cross-sectional area (CSA) (**A**), minimal (IMIN) (**B**) and maximal (IMAX) (**C**) moments of inertia, and bending stiffness (BENDST-R) (**D**) are significantly reduced in patients with spinal cord injury and history of one or more leg fractures compared with ambulatory controls [63]. Further, although reduced, moment of inertia (minimum and maximum) values were not significantly different between controls and patients with spinal cord injury who had no fractures. These results demonstrate that structural analysis of the leg may contribute to estimation of fracture risk in this population. However, computed tomography scans are not commonly available for midtibia analysis, and currently this approach is not available in clinical practice. SCI—spinal cord injury; SCI-Fx—spinal cord injury with fracture.

# Theoretical Framework for Fracture Risk Prediction

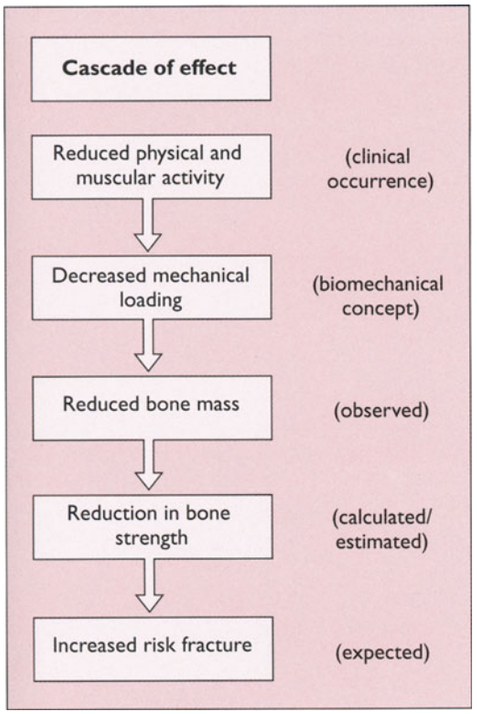


**FIGURE 13-30.** Cascade of effect summarizing the course of immobilization osteopenia. The result of an immobilizing disease or condition is regional paralysis and/or paresis or reduced physical activity and movement, relative to the extent of the immobilization. By definition, decreased activity means decreased habitual mechanical loading. The observed effect is regional bone loss, but other neurogenic or endocrine factors may also influence skeletal response. While bone mass is commonly used to represent bone strength, bone mineral density is only moderately correlated with breaking strength. However, geometric and architectural factors should not be ignored. Reduced bone mass and bone strength imply elevated fracture risk, but other components need additional consideration. First, we have little information about the structural and geometric bone responses to immobilization and whether compensatory mechanisms preserve bone strength. Second, we know little about the risk factors underlying fractures in patients with paralytic or immobilizing conditions. Specifically, these patients are not subjected to the same habitual loading patterns as ambulatory persons (*eg*, repetitive loading 1 to 1.5 times body weight during ambulation); thus, the interpretation of fracture risk based on bone mass may be inadequate in these populations.

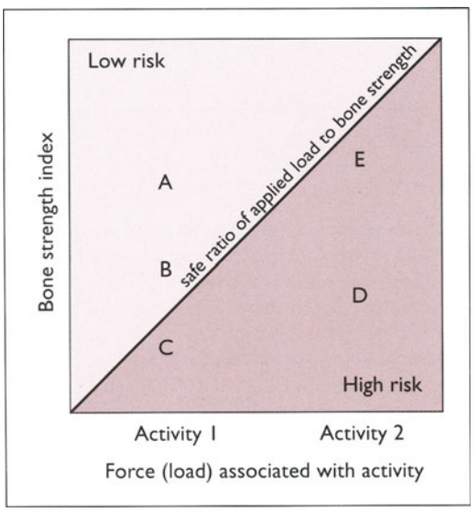


**FIGURE 13-31.** Risk profile comparing bone strength with fracture event. Does low bone mass indicate high fracture risk? For a fracture to occur, the applied load must be greater than the bone can withstand, and the type and location of fracture depend on characteristics of the loads applied to the skeleton as well as the strength of the bone. Essential data that influence the mechanical failure (fracture) of bone are the type, direction, and velocity of applied loads. Therefore, an event that would cause fracture in one individual might not produce the same effect in someone with stronger bones. Furthermore, the forces applied to the bone during various activities differ according to individual variables, such as weight, height, body segmental lengths and mass, and velocity during the activity.

This graph describes a theoretical approach for estimation of individualized fracture risk. Whether a given activity imparts a fracture risk depends on the force of the activity relative to the strength of the bone. For example, activity 1 may represent falling out of a wheelchair. This imposes no risk to person A (ambulatory person) or person B (person with spinal cord injury) because both have bones that are strong enough to withstand the force of the fall. Person C (person with spinal cord injury), however, is expected to sustain a fracture during the fall because his bone strength is below the safe level (*ie*, the applied load exceeds the bone failure strength). Thus, the clinician must be aware of the heightened fracture risk that might be associated with activities that would pose no risk for ambulatory individuals, such as stretching a leg or lower-extremity dressing. Precautions can be suggested to reduce the applied loads (*eg*, "don't pull your leg so hard during stretching exercise") and reduce fracture risk. Conversely, some activities involve high loads, and the bone would be expected to fracture regardless of bone strength. Activity 2 may represent a motor vehicle accident in which the applied loads exceed bone strength in both person D (person with spinal cord injury) and person E (ambulatory person). Risk prediction based on bone mass would be pointless in this case.

In summary, bone fracture occurs when the applied load exceeds the bone strength, and bone does not fracture when bone strength is greater than the applied load. Although calculation of individualized risk profiles is not readily available, a general awareness of this approach should be useful in clinical interactions with patients to guide prevention.

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# 14

# *Etiology and Biomechanics of Hip and Vertebral Fractures*

*Mary L. Bouxsein and Karl J. Jepsen*

Fractures are one of the most dramatic and devastating sequelae of the aging of the human skeleton. In the United States alone, more than 1.5 million age-related fractures occur annually, including 300,000 hip and 500,000 vertebral fractures. Associated medical expenditures amount to nearly $14 billion annually. Moreover, on the basis of current demographic trends, which predict a dramatic increase in the number of individuals older than 70 years of age, the number of fractures is projected to double or triple in the next 50 years [1]. Clearly, interventions for reducing the incidence of fracture are needed. To be most effective, these interventions must be based on a sound understanding of the cause of fractures. In the past, the predominant view was that age-related fractures were strictly a consequence of bone loss. This view was based on studies showing a dramatic increase in fracture incidence with age and a greater fracture rate in women than in men *(see* Chapter 1). However, recent evidence indicates that factors related not only to skeletal fragility but also to skeletal loading influence the risk of fracture.

This chapter reviews the cause of age-related fractures of the hip and spine, discusses basic concepts in bone biomechanics, presents age-related changes in bone properties, introduces a standard engineering concept used to evaluate structural failures, and applies this concept to skeletal fractures. Integrated into the discussion are concepts related to both skeletal loading and skeletal fragility.

# Basic Bone Biomechanics

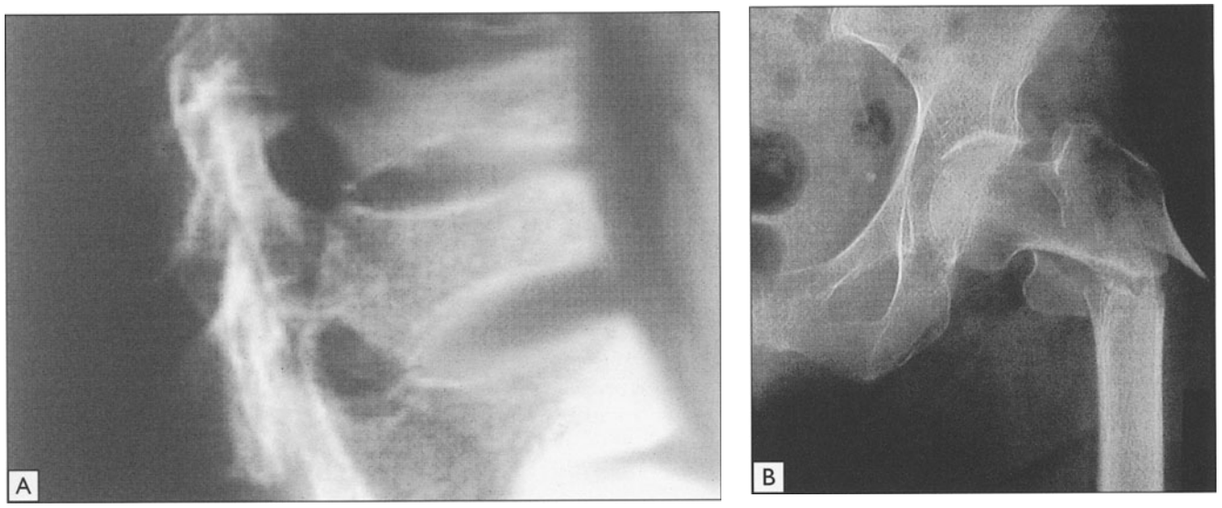



**FIGURE 14-1.** Definition of fracture. **A,** Vertebral compression fracture. **B,** Fracture of the femur. Although it is not entirely clear why bone fails, in general bone will fail when the applied load generates an internal stress that exceeds the strength of the underlying tissue. Alternatively, and equally important, failure can also occur when the energy or work imparted to the skeleton exceeds the energy-absorbing capacity or toughness of the underlying skeletal structure.

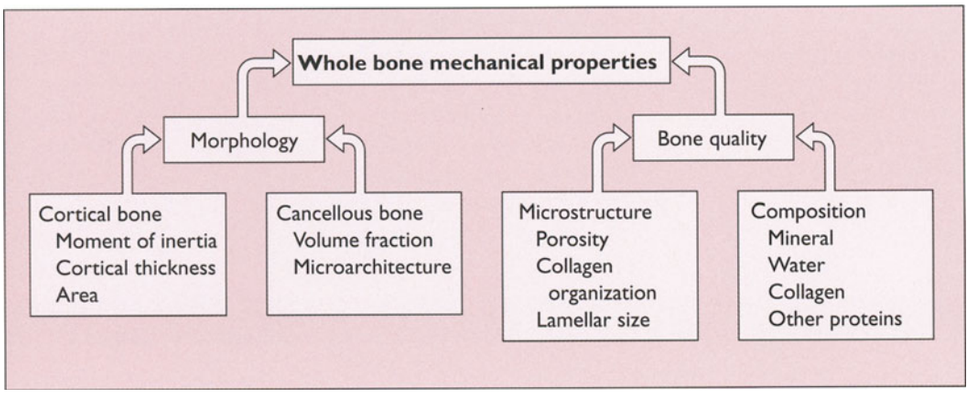



**FIGURE 14-2.** Relationship between mechanical properties of bone and skeletal traits. For all structures, whole bone mechanical properties, such as stiffness, failure load, and work-to-failure, depend on the size and shape (morphology) of the structure and the mechanical properties (quality) of the underlying tissue. *Bone quality* refers to a wide range of tissue-level mechanical properties, such as strength, modulus, toughness, and fatiguability. Thus, the failure of a skeletal structure depends on changes that occur to any of these underlying skeletal traits.

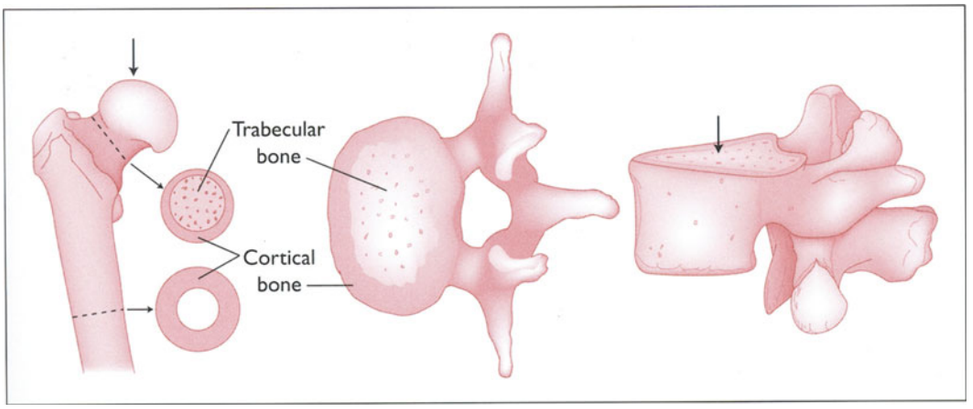
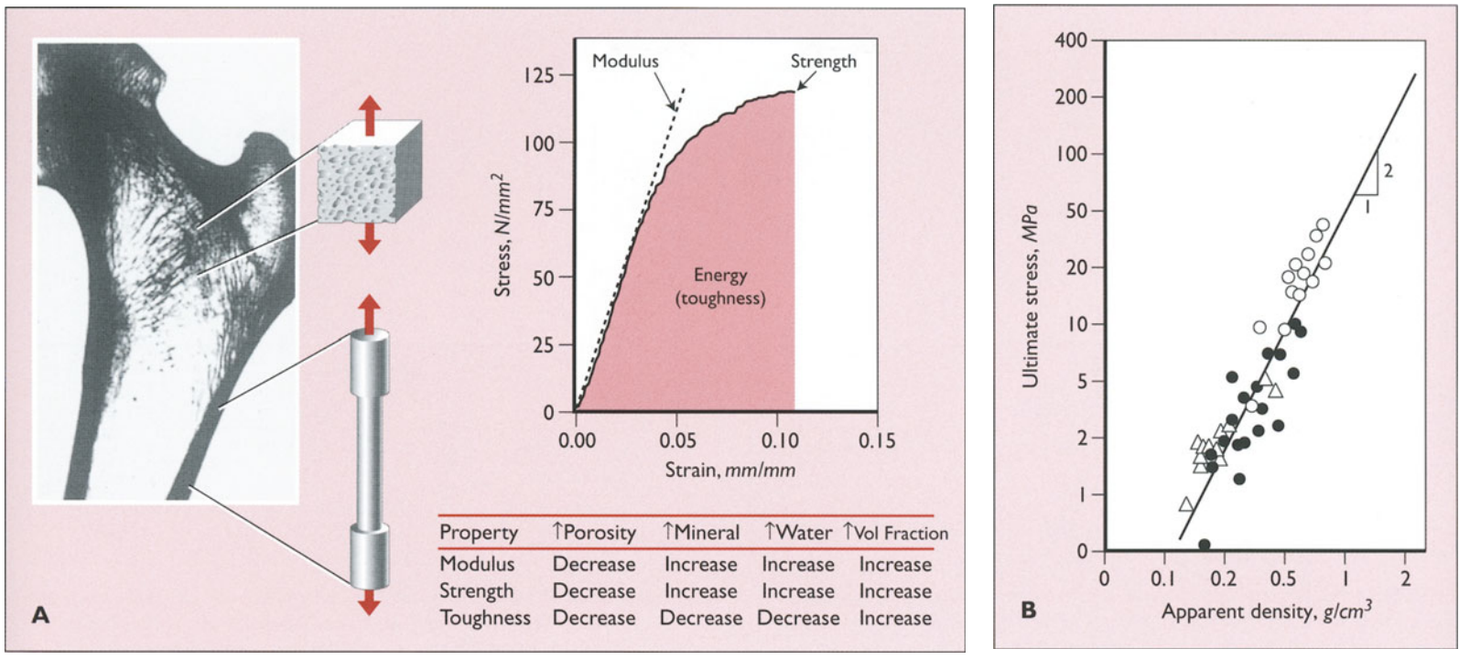



**FIGURE 14-3.** Effect of bone size and shape on its ability to resist failure. For the spine, which is subject largely to compressive loads during normal daily activities, a morphologic trait that plays an important role during loading is cross-sectional area. For the proximal femur, which is subject to a combination of compressive, bending, and torsional loads, the morphologic trait that acts to resist these loads is the moment of inertia. The moment of inertia, in contrast with area, which measures the amount of tissue, is a measure of the spatial distribution of tissue.




| Property | ↑Porosity | ↑Mineral | ↑Water | ↑Vol Fraction |
|---|---|---|---|---|
| Modulus | Decrease | Increase | Increase | Increase |
| Strength | Decrease | Increase | Increase | Increase |
| Toughness | Decrease | Decrease | Decrease | Increase |

**FIGURE 14-4. A,** The mechanical properties of cortical and cancellous bone tissues can be determined by "machining" samples of each tissue type and subjecting these samples to a battery of standard mechanical tests. The test most commonly used is the monotonic test to failure. The stress (a measure of force intensity) and strain (a measure of relative displacement) data generated from the experiment are used to estimate the mechanical properties of the bone tissues, such as tissue stiffness (modulus), strength, and work-to-failure (toughness). These mechanical properties are defined by the composition and microstructure of the underlying matrix. Thus, variations in these matrix traits will result in alterations in each tissue mechanical property. **B,** The strong relationship between density and the mechanical behavior of trabecular bone. The relationship between these two variables is linear on a log-log scale and therefore can be described by a power law of the form $y = ax^b$. Several studies have shown that the exponent $b$ is approximately 2. Therefore, small changes in density can result in dramatic changes in compressive strength. For example, a 25% decrease in apparent density, approximately equivalent to 20 to 25 years of age-related bone loss, would be predicted to cause an approximately 45% decrease in the compressive strength of trabecular bone. *(Adapted from* Carter and Hayes [2].)

## Age-Related Changes in Bone

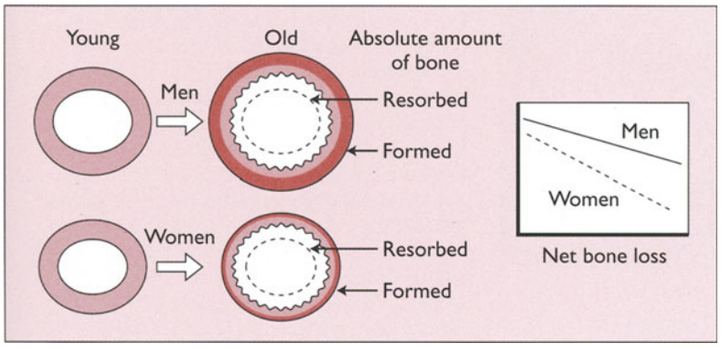
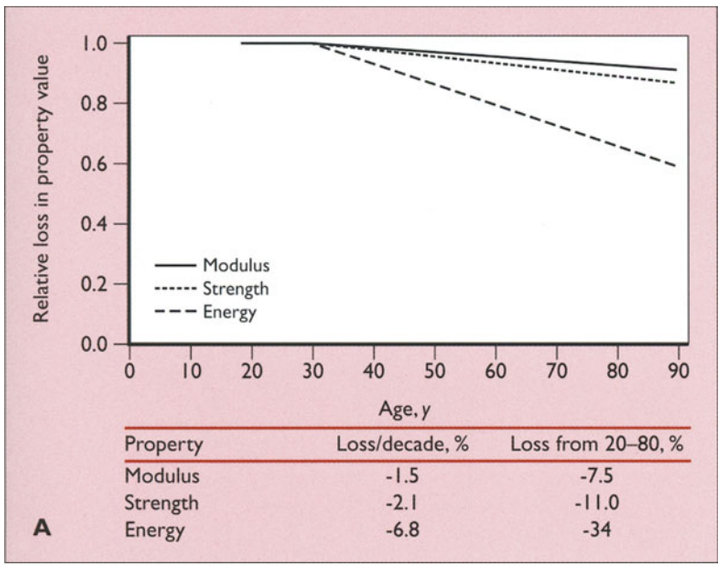
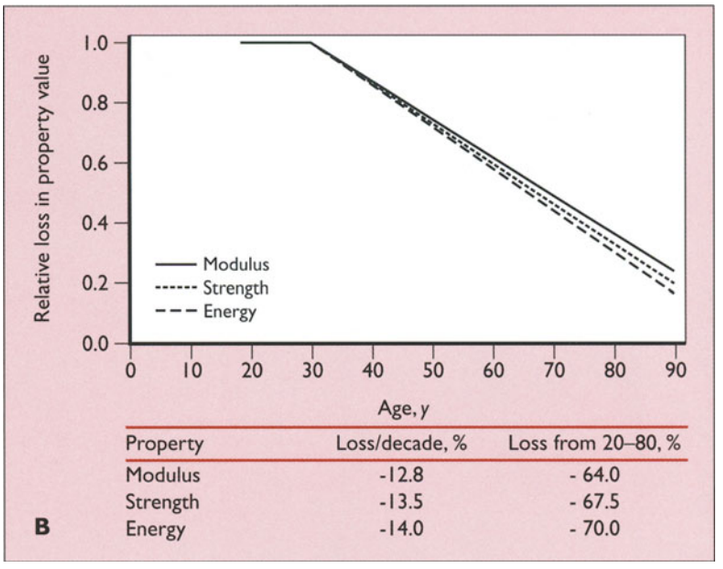



**FIGURE 14-5.** Age-related changes in the cross-sectional geometry of the femoral midshaft. In general, whereas both women and men undergo periosteal apposition with aging, the absolute amount of bone gained in men is greater than that in women [3]. These geometric adaptations increase the cross-sectional moment of inertia of the specimen and lead to an increased resistance to bending and torsional loads and probably help to offset the detrimental effects of an age-related increase in intracortical porosity, which tends to weaken the bone. Women with hip fractures have decreased cross-sectional area of the femoral neck and thinner cortices [4, 5], perhaps indicating that these individuals have a decreased ability to undergo this structural compensation with aging. Moreover, the amount of endosteal bone resorption with aging is relatively greater in women than in men. Taken together with lesser periosteal bone accumulation, this results in a greater weakening of diaphyseal bone strength in aging women. The structural differences between individuals with fractures and those who are fracture free, and between women and men, most probably have their origins in growth as well as aging, since to a larger extent it is during growth that adult bone morphology is determined [3]. (*Adapted from* Seeman [3].)




| Property | Loss/decade, % | Loss from 20–80, % |
|---|---|---|
| Modulus | -1.5 | -7.5 |
| Strength | -2.1 | -11.0 |
| Energy | -6.8 | -34 |




| Property | Loss/decade, % | Loss from 20–80, % |
|---|---|---|
| Modulus | -12.8 | - 64.0 |
| Strength | -13.5 | - 67.5 |
| Energy | -14.0 | - 70.0 |

**FIGURE 14-6.** Age-related changes in the material properties of cancellous and cortical bone. **A,** Age-related changes in the stiffness, strength, and energy-to-failure of human femoral cortical bone in tension. These data indicate that the intrinsic mechanical properties of cortical bone decrease with age and that cortical bone therefore weakens. Importantly, the dramatic age-related reduction in energy-to-failure indicates that cortical bone becomes more brittle with age. Thus, in normal individuals, the stiffness and strength of cortical bone decrease by approximately 8% to 11% from 20 to 80 years of age, whereas the energy to failure declines 34% [6]. **B,** Age-related changes in the mechanical properties of human vertebral trabecular cancellous bone tissue. To study age-related changes in vertebral trabecular bone, Mosekilde *et al.* [7] collected cadaveric vertebrae from 42 persons aged 15 to 87 years. Trabecular bone specimens, oriented either parallel or perpendicular to the superior-inferior axis, were removed from the vertebral bodies and tested in compression. A strong relationship was seen between age and density, ultimate strength, elastic modulus, and the energy absorbed before failure. The density decreased approximately 9% per decade, whereas the mechanical properties decreased 12% to 15% per decade [7].

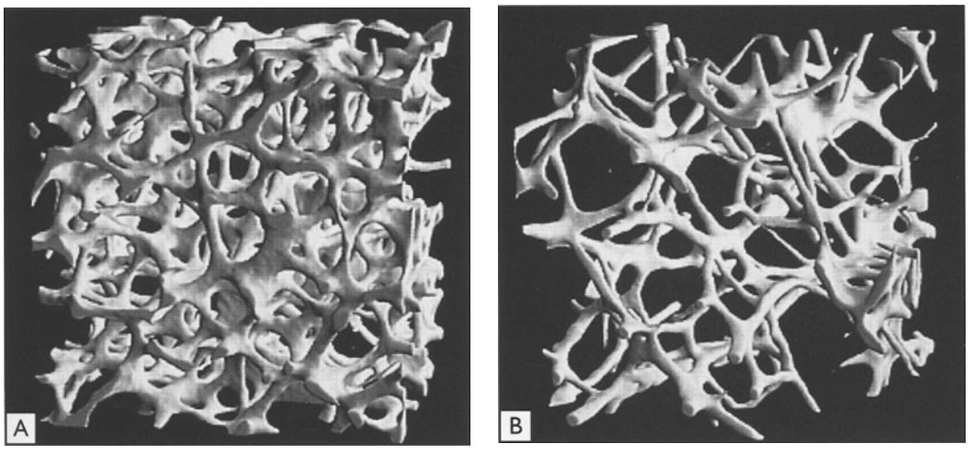



**FIGURE 14-7.** Dramatic age-related change in bone mass and architecture of vertebral trabecular bone. Trabecular bone strength depends not only on its density (Fig. 14-4B) but also on the arrangement and structure of the trabecular elements themselves. This trabecular architecture can be described by the number, orientation, spacing, thickness, and connectivity of trabeculae. This figure clearly shows that the changes in the architecture of trabecular bone accompany the age-related changes in bone density (42-year-old man [L2 level] [**A**] compared with 84-year-old woman [L2 level] [**B**]). The thickness and number of trabecular elements decrease, and the spacing between trabeculae increases, with a resulting decrease in density. In addition, there may be an accentuated loss of trabeculae that are oriented horizontally. It may be useful to picture the vertical trabeculae as columns that support compressive loads and to view the horizontal trabeculae as cross-struts that brace the columns. In this scenario, the thinning or loss of horizontal trabeculae would reduce the stability of the vertical trabecular "columns" and may lead to failure of the vertical trabeculae by buckling. The contribution of trabecular bone to overall bone strength varies with skeletal site. For example, by mass, the proportion of trabecular bone is approximately 60% to 90% at the vertebral body, 50% at the intertrochanteric region of the hip, 25% at the femoral neck, and less than 5% at the femoral and radial diaphyses [8]. *(Courtesy of* Dr. Ralph Müller, ETH, Zurich, Switzerland).

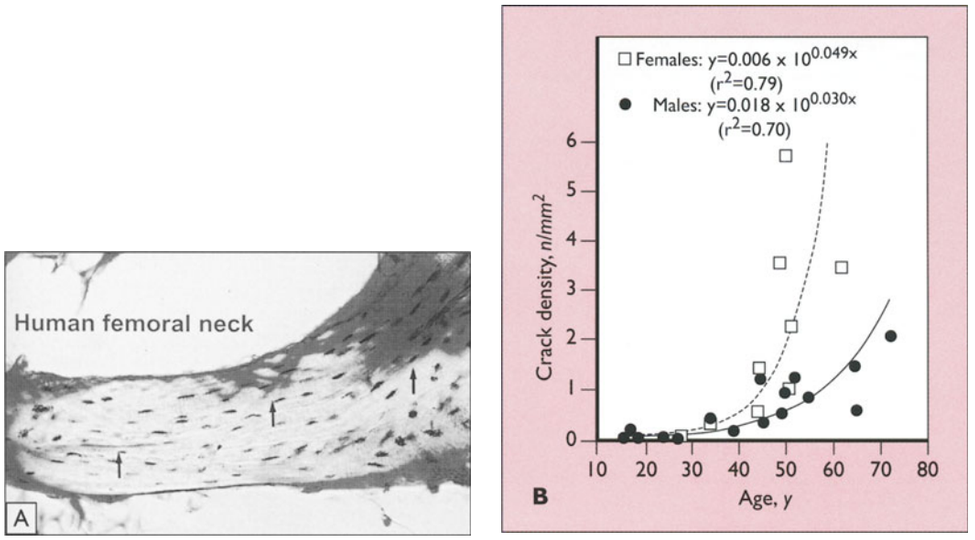
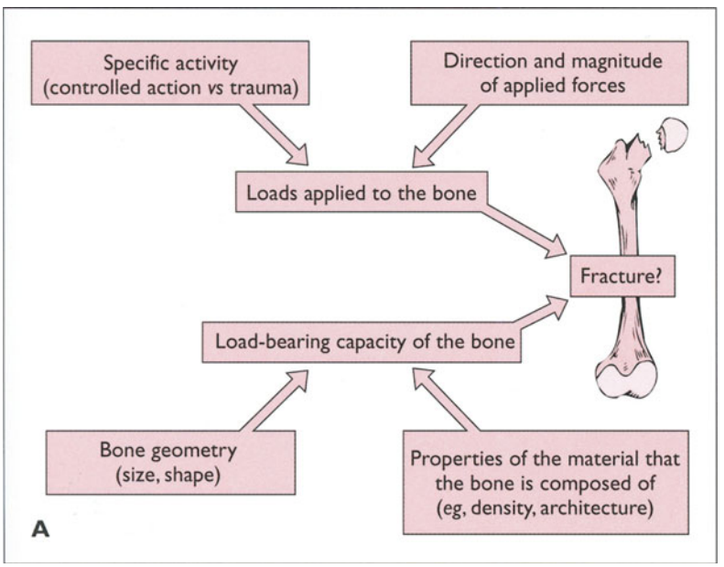



**FIGURE 14-8.** (see Color Plate) Age-related changes in microdamage accumulation in human cortical bone. Following repetitive loading, small cracks may develop in many materials. **A,** Small cracks in cortical and trabecular bone tissue, termed *microdamage*, have been identified using histologic techniques [9]. In excised bone specimens, an accumulation of microdamage leads to a decrease in the mechanical properties of the specimens. Microdamage has been observed in human cadaveric specimens from the femur and spine [10–12]. **B,** In one study, data from human cadaveric femurs suggest that the prevalence of microdamage increases dramatically with age, as measured by the concentration of microcracks in the femoral cortex [10]. This damage accumulation occurred about twice as rapidly in women as in men. Although it has been speculated that this may contribute to the higher fracture incidence in women than in men, there are no data to suggest a direct relationship between microdamage accumulation and fracture risk in humans [12].

## Determinants of Fracture Risk and Introduction of the Factor of Risk



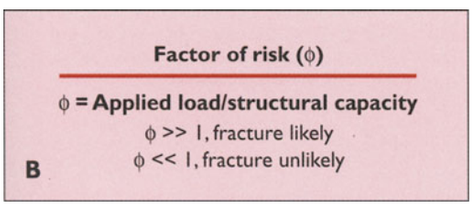




**FIGURE 14-9.** Factor of risk for fracture. **A**, Bone failure occurs when the load applied to a bone generates an internal stress that exceeds the strength of the underlying tissue. It is therefore obvious that skeletal loading is ultimately an important determinant of fracture risk. **B**, To express the related roles of skeletal loading and skeletal fragility, Hayes [13,14] introduced the concept of the factor of risk. The numerator of the factor of risk is the force applied to a bone during a given activity of interest, and the denominator is the structural capacity (or failure load) of the bone during that same activity. When this ratio is greater than 1 *(ie,* the force applied to the bone is much higher than the structural capacity of the bone), a fracture is predicted to occur. A high factor of risk may result from low bone mineral density and therefore very weak bones, or it may occur when high forces are applied to the skeleton, such as during a motor vehicle accident or a fall. For example, to implement the factor of risk concept for hip fractures, it is essential to 1) identify activities associated with a hip fracture, 2) determine the loads applied to the proximal femur during those activities, and 3) estimate the failure load of the proximal femur during those activities.

# Biomechanics of Hip Fractures

**MULTIPLE LOGISTIC REGRESSION ANALYSIS OF FACTORS ASSOCIATED WITH HIP FRACTURE IN COMMUNITY-DWELLING MEN AND WOMEN WHO FELL**

| Factor | Adjusted Odds Ratio | (95% Confidence Interval) | P Value |
|---|---|---|---|
| Fall to the side | 5.7 | (2.3–14) | <0.001 |
| Femoral neck bone mineral density* | 2.7 | (1.6–4.6) | <0.001 |
| Potential energy of fall† | 2.8 | (1.5–5.2) | <0.001 |
| Body mass index* | 2.2 | (1.2–3.8) | 0.003 |

*Calculated for a decrease of 1 standard deviation.
†Calculated for an increase of 1 standard deviation.

**FIGURE 14-10.** Investigation of the interactions between fall severity and bone mineral density as risk factors for hip fracture risk. Risk factors associated with hip fracture in community-dwelling men and women who fell [15]. This case-control study demonstrates that fall severity and bone mineral density are *independent* risk factors for hip fracture. In a case-control study of 149 community-dwelling men and women, 72 persons fell and sustained a hip fracture (case-patients) and 77 persons fell and did not sustain a hip fracture (controls). Multiple logistic regression analysis of the data showed that in the case-patients, characteristics related to fall severity, femoral bone mineral density (BMD), and body habitus were strong and independent risk factors for hip fracture. For example, persons who fell to the side were six times more likely to sustain a hip fracture than were persons who fell in any other direction. In agreement with other prospective studies of fracture risk [16–18] the risk of hip fracture increased nearly three times for every 1–standard deviation decrease in femoral BMD compared with the mean BMD, and approximately doubled for each standard deviation decrease in body mass index [19]. These findings emphasize the concept that some important determinants of hip fracture risk are not captured in a BMD measurement.

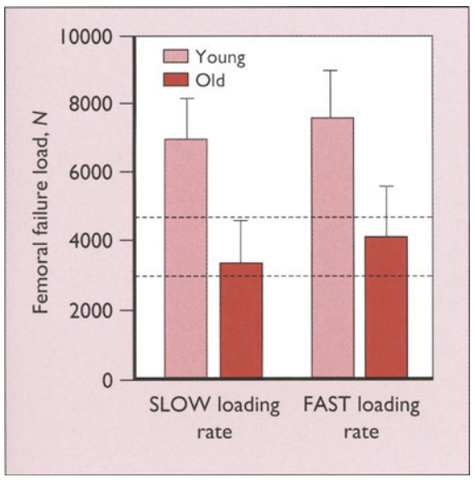



**FIGURE 14-11.** Influence of age and loading rate on the strength of human cadaveric femurs. Mean failure loads for cadaveric proximal femurs from young *(light shading)* and elderly *(dark shading)* donors. The femurs were mechanically tested to failure at slow (2 mm/sec) and fast (100 mm/sec) loading rates in a configuration designed to simulate a sideways fall with impact to the greater trochanter [20,21]. For both the slow and the fast loading rates, femurs from the young donor group were 80% to 100% stronger than femurs from elderly individuals. Femurs from both the young and the elderly group were approximately 20% to 30% stronger, and absorbed 20% to 30% more energy when tested at the fast loading rate than when tested at the slow loading rate. The two dashed horizontal lines represent the 95% confidence interval for the load that is predicted to be applied to the femur during a sideways fall from standing height. Thus, this cadaveric study indicates that most elderly individuals would be at high risk for hip fracture during a fall from standing height because the load applied to the femur is close to or exceeds the load required to break it. (*Adapted from* Courtney *et al.* [20,21].)

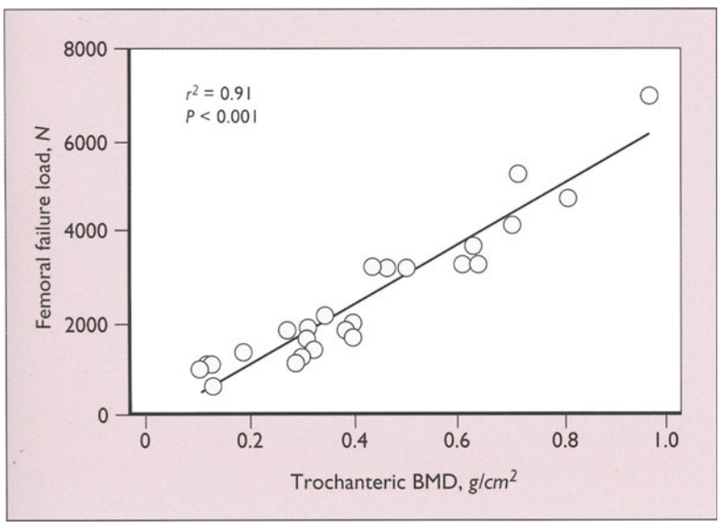



**FIGURE 14-12.** Relationship between bone mineral density and femoral strength. Trochanteric bone mineral density (BMD) and femoral failure load of cadaveric proximal femurs. There is a strong linear relationship between femoral BMD and the failure load of elderly cadaveric femurs tested in a configuration designed to simulate a fall to the side with impact to the greater trochanter. The load required to fracture the elderly proximal femur ranges from approximately 800 to 7000 N (or about 200 to 1700 pounds).

# Biomechanics of Vertebral Fractures

**RESULTS OF SURVEY OF PATIENTS WITH VERTEBRAL FRACTURE**

| Activity | Patients, % |
|---|---|
| Controlled (eg, lifting) | 25 |
| Fall | 55 |
| Slow onset/unknown | 19 |

**FIGURE 14-13.** Circumstances associated with vertebral fracture. It has always been understood that only a small fraction of vertebral fractures are acutely symptomatic and cause the patient to seek medical assistance. However, only recently have large-scale clinical trials estimated the relative incidence of symptomatic and asymptomatic fractures. Results from the Fracture Intervention Trial (FIT), representing the experience of 2000 elderly women who had already sustained at least one vertebral fracture, now address this question [22]. Among approximately 1000 women assigned to receive placebo, new vertebral fractures occurred at an annual rate of 18%, as determined by periodic follow-up spine radiographs. By contrast, the annual incidence of clinically evident fractures was only 6%. Thus, patients are not aware of two of every three vertebral compression fractures at the time the fracture occurs. Consequently, understanding of the antecedent events that contribute to fracture must remain incomplete. In one study of consecutive patients reporting to an emergency department with vertebral fracture, patients underwent a structured interview within 1 week of the event to ascertain activities associated with fracture [23]. The prevalence of falls in these patients is surprisingly high. Thus, efforts aimed at preventing falls should be undertaken to prevent both hip and vertebral fracture.

**PREDICTED COMPRESSIVE LOADS ON THE L2 AND T11 VERTEBRAE DURING VARIOUS ACTIVITIES**

| | Predicted Load on T11 | | Predicted Load on L2 | |
|---|---|---|---|---|
| Activity | N | Body Weight, % | N | Body Weight, % |
| Relaxed standing | 240 | 41 | 290 | 51 |
| Rising from a chair, without use of hands | 340 | 60 | 980 | 173 |
| Standing, holding 8 kg of weight close to body | 320 | 57 | 420 | 74 |
| Standing, holding 8 kg of weight with arms extended | 660 | 117 | 1302 | 230 |
| Standing, trunk flexed 30°, arms extended | 370 | 65 | 830 | 146 |
| Standing, trunk flexed 30°, holding 8 kg of weight with arms extended | 760 | 135 | 1830 | 323 |
| Lift 15 kg of weight from floor, knees bent, arms straight down | 593 | 104 | 1810 | 319 |

**FIGURE 14-14.** Predicted compressive loads on the second lumbar (L2) and 11th thoracic (T11) vertebrae during various activities. To further understand the factors that contribute to vertebral fracture risk, Wilson *et al.* [24] used a mathematical model of the spine to estimate the compressive loads on the thoracic and lumbar vertebrae during activities of daily living. For example, rising from a chair without the use of one's hands was predicted to generate a compressive load on the second lumbar vertebrae equal to 173% of one's body weight. The compressive load applied to the lumbar vertebrae during lifting approximately 30 lbs from the floor by bending at the waist is predicted to be three times an individual's body weight. The loads were computed for a woman who weighs 58 kg and is 162 cm tall [24]. N—newtons.

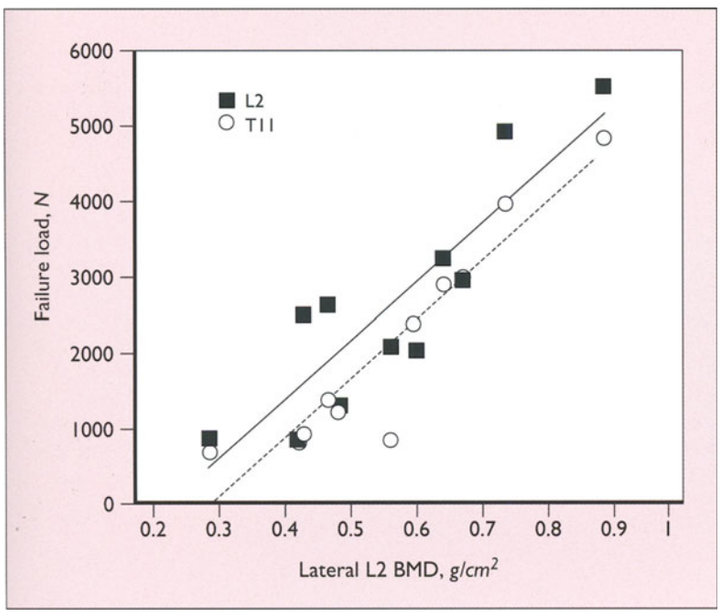



**FIGURE 14-15.** Linear relationship between lumbar spine bone mineral density (BMD) and compressive failure loads of the thoracic and lumbar vertebral bodies. Cadaveric spines from elderly donors (mean age, 72 years; range, 48–87) were subjected to compressive forces to determine their load-bearing capacity and to determine the relationship between lumbar BMD and the failure loads of both lumbar and thoracic vertebral bodies [25]. Vertebral bodies were obtained from the T10-T12 and L1-L3 regions of 25 elderly cadaveric spines (15 women, 10 men; 64 to 95 years of age). Bone mineral density was measured in each specimen with dual-energy x-ray absorptiometry (DEXA). Specimens were tested to failure in a forward-bending configuration to determine the failure load. There was a strong relationship between lumbar spine BMD and failure loads of T11 and L2 ($r = 0.94$, $P < 0.001$; and $r = 0.89$, $P < 0.001$; respectively). The failure loads ranged from approximately 800 to 5800 Newtons (*N*). These findings indicate that lumbar spine BMD, in general, is a reasonably good predictor of the load-bearing capacity of both thoracic and lumbar vertebral bodies, at least when analyzed over a fairly broad range of BMD values. However, it should be noted that the standard error of the estimate (*ie*, the error that could be expected when one is trying to predict the failure load of an individual vertebral body from a single BMD value) was substantial. Moreover, although suggestive, this type of study cannot address directly how *changes* in BMD would affect vertebral strength. (*Adapted from* Moro *et al.* [25].)

**FACTOR OF RISK FOR VERTEBRAL FRACTURE ASSOCIATED WITH COMMON ACTIVITIES**

| | Bone Mineral Density, $g/cm^2$ | | | | | | |
|---|---|---|---|---|---|---|---|
| **Activity** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** |
| Get up from sitting | **1.5** | 0.6 | 0.4 | 0.3 | 0.2 | 0.2 | 0.2 |
| Lift 15 kg of weight with knees straight | **2.6** | **1.1** | **0.7** | 0.5 | 0.4 | 0.3 | 0.3 |
| Lift 30 kg of weight with knees straight | **3.7** | **1.5** | **1.0** | **0.7** | 0.6 | 0.5 | 0.4 |
| Lift 30 kg of weight with deep knee bend | **3.0** | **1.3** | **0.8** | 0.6 | 0.5 | 0.4 | 0.3 |
| Open window with 50 N of force | **1.1** | 0.5 | 0.3 | 0.2 | 0.2 | 0.1 | 0.1 |
| Open window with 100 N of force | **1.4** | 0.6 | 0.4 | 0.3 | 0.2 | 0.2 | 0.2 |
| Tie shoes while sitting down | **1.4** | 0.6 | 0.4 | 0.3 | 0.2 | 0.2 | 0.2 |

**FIGURE 14-16.** Factor of risk for vertebral fracture associated with common activities, as a function of lumbar bone mineral density (BMD). The numerator of the factor of risk was determined from models of spine loading at L2 for an elderly woman of average height and weight. The denominator was determined from regression analysis between lateral lumbar BMD and the load-bearing capacity of the L2 vertebrae. The values for lateral BMD cover a wide range of densities, in particular very osteopenic individuals. The t-score (number of standard deviations from the mean value for BMD in young women) is approximately +1 for a BMD of 0.9 $g/cm^2$ and is –5 for a BMD of 0.4 $g/cm^2$. The factor of risk is predicted to be greater than or close to 1 for low BMD values (*shown in bold*). These results indicate that common activities of daily living, such as shoe tying or rising from a chair, can place persons in the lowest BMD categories at high risk for fracture. *(Adapted from* Myers and Wilson [26].)

# Fracture Prevention

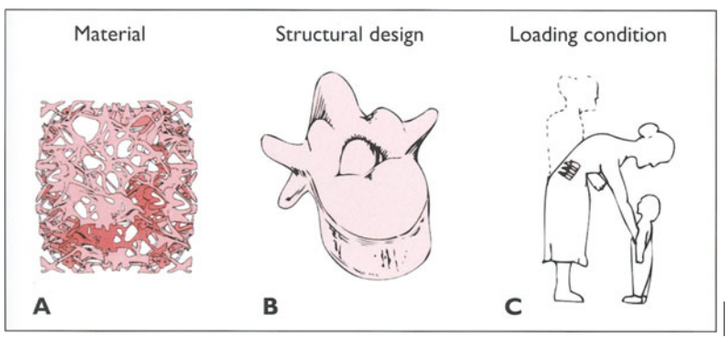



**FIGURE 14-17.** Factors that determine the amount of force a skeletal structure can withstand. In this figure, the vertebral body is used to demonstrate the characteristics of the spine that determine its capacity to resist mechanical loads. The ability of a structure to carry loads is determined by the intrinsic material that makes up the structure, the corresponding mechanical behavior of that matter, the way that the matter is arranged to form a skeletal structure, and the loading conditions to which the structure is subjected. In the spine, the vertebral bodies carry a large proportion of the compressive loading. The vertebral body consists primarily of trabecular bone (**A**). The structural design of the vertebral body is determined by the organization of this trabecular bone and by the size and shape of the vertebral body itself (**B**). Finally, the behavior of the structure is also determined by the loading conditions that arise from activities of daily living (**C**) or from traumatic loading situations *(eg,* falls or motor vehicle accidents). *(Adapted from* Myers and Wilson [26].)

**FRACTURE PREVENTION STRATEGIES**

- Maintain or increase bone strength
  - Exercise
  - Diet
  - Pharmacologic interventions
    - Antiresorptive (estrogen, SERMs, calcitonin, and bisphosphonates) and anabolic agents (fluoride, parathyroid hormone)
- Reduce the loads applied to bone
  - Decrease fall frequency
  - Decrease fall severity
  - Avoid lifting/bending activities
  - Use proper lifting techniques

**FIGURE 14-18.** Strategies for prevention of fractures. Based on the concept of the factor of risk, two complementary strategies could be used to reduce the risk of fracture: 1) improve bone strength (*ie,* improve the quantity and quality of bone) and 2) reduce the loads applied to the bone. The first approach requires attention to standard interventions, such as dietary adequacy, supplemental calcium and vitamin D use, regular frequent physical exercise, and various pharmacologic interventions (see Chapters 15 to 17). The second approach requires interventions aimed at reducing loads applied to bone via decreasing the risk of falling, decreasing the severity of falls that do occur, and minimizing damage caused by routine activities. Leg muscle weakness is an independent risk factor for falls and hip fracture; thus, a cautious program of progressive-resistance strength training is an attractive option. Although such a program does not consistently provide important gains in bone mineral density, it can lead to striking gains in muscle strength that are accompanied by improved performance of tasks, such as rising from a chair and walking [27]. SERM—selective estrogen receptor modulator.

**REDUCTION IN HIP FRACTURE RISK WITH TROCHANTERIC PADDING**

| Type of Fracture | Hip-Protector Group, *n/1000 person-y* | Control Group, *n/1000 person-y* | Relative Hazard (95% Confidence Interval) |
|---|---|---|---|
| Hip fracture | 21.3 | 46.0 | 0.4 (0.2–0.8)* |
| Pelvic fracture | 3.3 | 8.2 | 0.4 (0.1–1.8)† |
| Other fractures of the legs or trunk | 21.3 | 20.6 | 1.0 (0.5–2.0)† |
| Fracture of the arms | 16.4 | 19.9 | 0.8 (0.4–1.7)† |

**P = 0.008 for comparison between hip-protector group and control group.*
*†P ≥ 0.05 for comparison between hip-protector group and control group.*

**FIGURE 14-19.** Trochanteric padding reduces hip fracture risk. Wearing padding directly over the greater trochanter is an interesting strategy aimed at minimizing the force of a fall that is transmitted to the bone. To be effective, a padding system must attenuate forces under real-world impact conditions, must be worn by vulnerable patients, and must be able to reduce impact force below the level at which a fracture would be predicted to occur. Robinovitch *et al.* [28] performed testing of various trochanteric padding systems, demonstrating the ability of the pads to reduce the impact force applied to the femur during a sideways fall. In support of these laboratory findings, several prospective studies have demonstrated that use of trochanteric padding systems can dramatically reduce the risk of hip fracture in frail elderly adults [29–31]. The figure shows results from one study, in which 1800 ambulatory but frail elderly were randomly assigned either to a group that wore a hip protector or to a control group [30]. These individuals were followed for the incidence of falls and fractures of the hip and other sites. The rates of hip fracture in the hip protector and control groups, respectively, were 21.3 and 46.0 per 1000 person-years, representing a 54% reduction in hip fracture risk in the hip protector group. While these findings demonstrate the ability of hip protectors to reduce fracture risk among the frail elderly, compliance in wearing the pads was poor, highlighting an important challenge for clinical use of trochanteric padding devices.

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15

# Role of Nonpharmacologic Approach to Fracture and Osteoporosis

*Richard L. Prince*

In view of the extremely high rates of osteoporotic fracture occurring in all developed and many developing countries, a population-based nonpharmacologic approach to the treatment and prevention of fracture and osteoporosis has many attractions. The major reason for the increasing importance of a public health approach to osteoporotic fracture is the increasing longevity of both men and women. Average life expectancy in most developed countries is about 85 years for women and 78 years for men. The incidence rates for all fractures show a peak in adolescence and a rising age-specific incidence from approximately 50 years on in both men and women. Thus, nonpharmacologic public health prevention efforts should be directed to individuals at these two specific times of life.

In childhood, and especially in adolescence, while the skeleton is developing, lifestyle influences have been shown to increase bone mass in the short term. Some of these gains may be reflected in a higher peak bone mass. It is also important to realize that part of the reason for the peak in fractures in adolescence is related to skeletal insufficiency as well as excessive force applied as the result of accidents. Thus, improving skeletal integrity in childhood may contribute to fracture prevention in adolescence.

Although optimization of peak bone mass theoretically is important in the prevention of fracture in old age, fracture rates are, in fact, lowest in middle age. A more logical, cost-effective approach may be to prevent the loss of bone occurring in old age, thereby reducing fractures. Two general approaches should be considered. The first is to detect patients at high risk for fracture with the use of historical demographic factors and bone densitometry and treat these subjects with a pharmacologic agent, such as a bisphosphonate or estrogen. The other approach discussed here is to apply public health approaches to the whole population with the aim of decreasing common risk factors. It is probable that dietary intervention with calcium or vitamin D, or both, can reduce fracture rates by approximately 30%. The figures in this chapter elaborate on the mechanisms and probable effects of these interventions, which concentrate principally on diet and exercise.

## Overview of Bone Acquisition and Maintenance

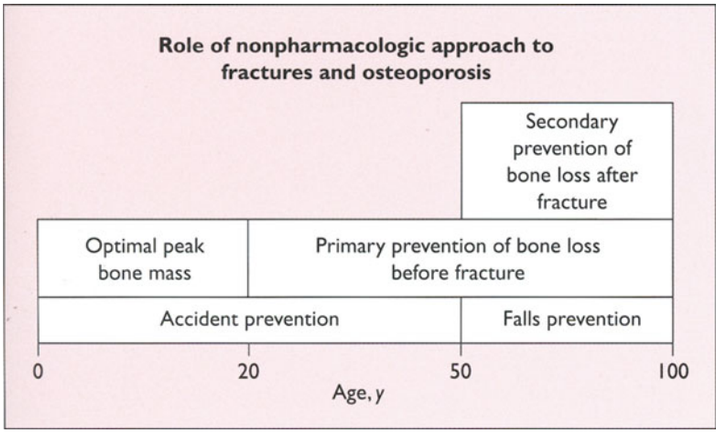



**FIGURE 15-1.** Role of nonpharmacologic approach to fractures and osteoporosis. Different interventions are needed at different times of life. A broadly based public health approach would include programs for reducing accidents in the earlier part of life and falls in the later part of life. Programs aimed at developing optimal peak bone mass and preventing bone loss before and after the first fracture also are integral to this overall approach.

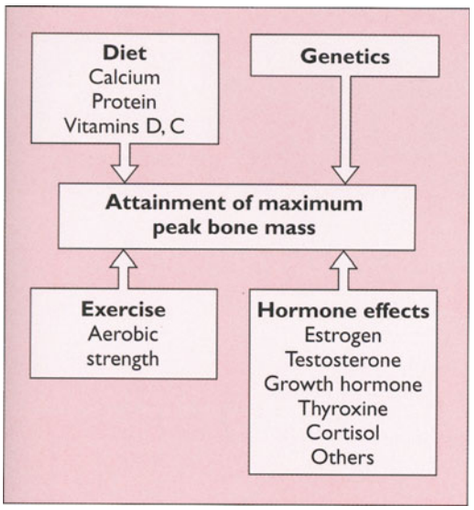



**FIGURE 15-2.** Attainment of maximal bone mass. Peak bone mass is attained at different ages at different sites of the skeleton. In the axial skeleton, it is usually attained at approximately 18 years of age. Periosteal bone formation continues in the appendicular skeleton until approximately the age of 25 years. Thus, factors affecting the development of peak bone mass must be considered until this age has been reached.

Environmental factors, such as diet and exercise, act only within the genetic limitations imposed on the individual. The genetic determinants of peak bone mass currently are an active area of research. It is clear that genetic variation is associated with differences in peak bone mass [1,2]. In addition, alterations of various hormones resulting from specific endocrine disorders can induce osteoporosis. Examples of these are deficiencies of estrogen, testosterone, and growth hormone. Similarly, excess production of hormones *(eg,* thyroxine and cortisol) can also impair skeletal integrity. Much more common than the hormonal deficiencies, however, are nutritional deficiencies and the effects of suboptimal exercise.

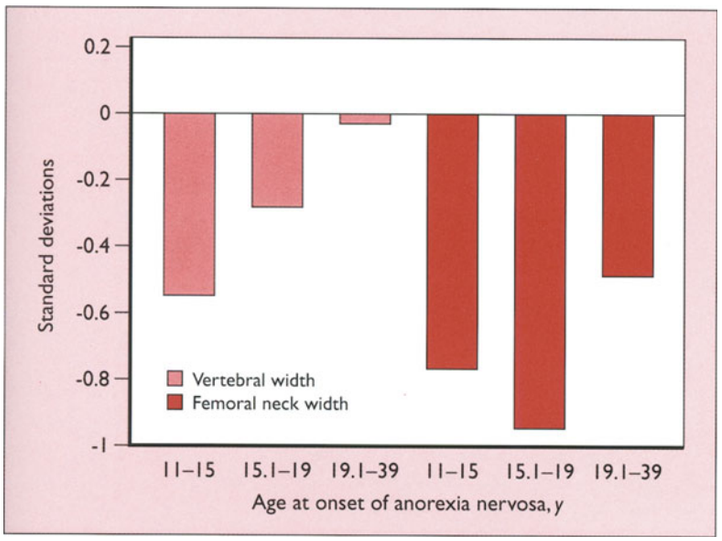



**FIGURE 15-3.** Bone size development. Bone size is an important determinant of strength. Like bone density development, bone size development also occurs rapidly in adolescence. Seeman *et al.* [3] showed that nutritional deficits that may impair gonadal function (in this case due to anorexia nervosa) during skeletal growth can have permanent effects on bone size. The figure shows the relative reductions (in standard deviation units) of vertebral and femoral neck width in women who had experienced the onset of anorexia nervosa at various ages compared with control women. Bones were smaller in those who developed the disorder at earlier ages, when skeletal growth was occurring. Thus, nutrition is important not only for bone mass accumulation but also for bone size development. Both characteristics affect bone strength. (*Adapted from* Seeman *et al.* [3]; with permission.)

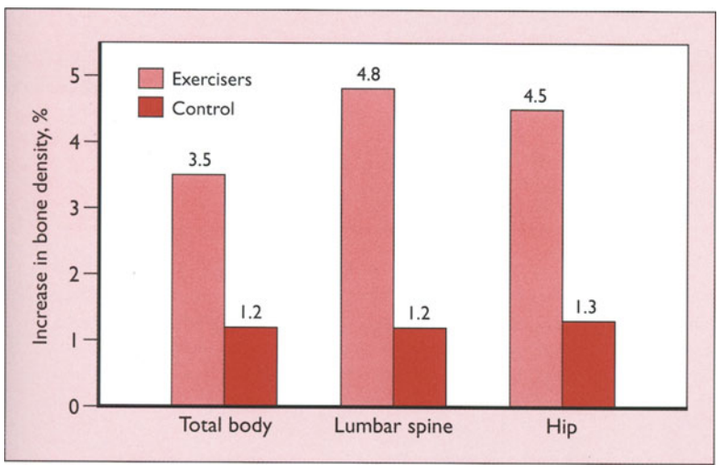



**FIGURE 15-4.** Effects of exercise in childhood. Data on exercise in childhood suggest that significant short-term increases in bone mass can be achieved by increasing forces on the skeleton within achievable limits. Regular physical activity for at least 1 hour three times per week should be considered as part of an exercise prescription for children [4].

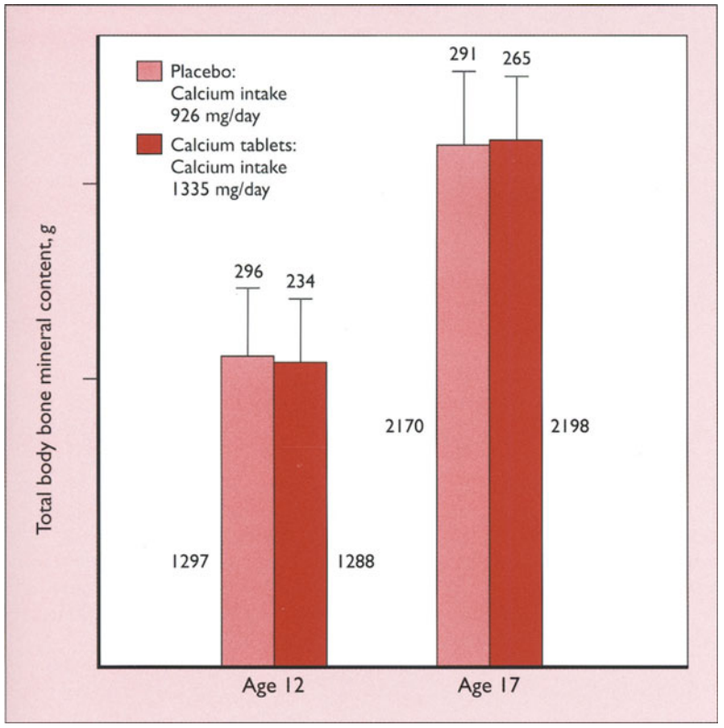



**FIGURE 15-5.** Effects of calcium supplementation in adolescent girls. The nutrient most fully investigated in relation to the growing skeleton is calcium. There is no agreement on the minimal calcium intake required, in part because there is no agreement as to the best determinant of clinically meaningful outcome. Much emphasis has been placed on short-term calcium balance studies. In these, the data point to small beneficial effects of increasing calcium intake from 800 to 1300 mg per day. These data have been criticized because the dependent variable—calcium balance—includes the independent variable—calcium intake—as a dominant factor in the calculation of balance. Furthermore, all the studies have been short term and may merely reflect delayed adaptation to low calcium intake. The delay may be related not only to a delay in increasing gut calcium absorption and renal calcium excretion but also to a delay in calcification of preformed osteoid.

Bone density has been used as an end point. Several studies have shown short-term gains in bone density that have not persisted when the calcium supplement was stopped. Thus, the clinical benefit is not clear. If such supplementation could reduce the incidence of childhood fractures, it might be a worthwhile intervention. If, however, the aim is to increase peak adult bone mass, the definitive answer to the question of optimal dietary calcium intake in childhood requires a long-term supplementation study. The only 5-year study showed no treatment benefit from increasing calcium intake from 980 to 1135 mg per day [5].

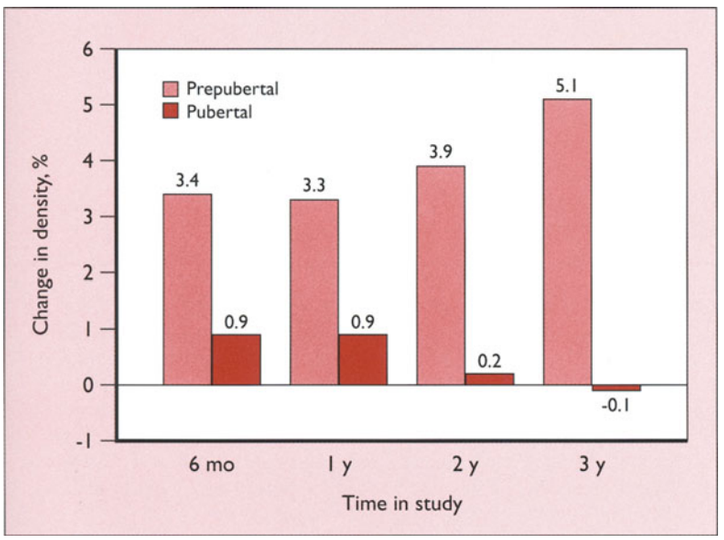



**FIGURE 15-6.** In younger children, there is evidence that dietary calcium supplementation is associated with an increase in bone mineral density. In a study by Johnston *et al.* [6] prepubertal and pubertal monozygous twins were randomly assigned to receive calcium supplements or placebo for 3 years. On average, the children who received supplements consumed 1612 mg of calcium/d, compared with 908 mg/d in the placebo group. The prepubertal twins receiving calcium supplements had higher bone density during the study than that of those receiving placebo, but the pubertal children experienced no benefit. There is evidence from other studies that the increase in bone density associated with calcium supplementation is not maintained if calcium intake is not continued at high levels, and the benefits of calcium supplementation on fracture risk in childhood or later, in adulthood, is not clear. (*Adapted from* Johnston *et al.* [6].)

**RECOMMENDED INTAKES OF CALCIUM AND VITAMIN D**

| | Age, y | Intake per Day |
|---|---|---|
| Calcium | 1–3 | 600 mg |
| | 4–8 | 1000 mg |
| | 9–18 | 1600 mg |
| | 19–50 | 1200 mg |
| | ≥50 | 1400 mg |
| Vitamin D | ≤50 | 200 IU |
| | 50–70 | 400 IU |
| | ≥70 | 600–800 IU |

**FIGURE 15-7.** Recommended intakes of calcium and vitamin D. The US National Academy of Sciences examined the available information on calcium and vitamin D requirements in children, and Heaney [7] developed recommendations based on these findings and previous estimates of optimal calcium intakes developed in a National Institutes of Health consensus conference. Although the evidence is limited, the recommended oral intakes should provide calcium and vitamin D adequate for skeletal development. Vitamin D deficiency may cause osteomalacia and rickets in children, especially in higher latitudes where sunlight exposure is restricted. (*Adapted from* Heaney [7].)

**PREVENTION OF CHILDHOOD FRACTURE BY PREVENTION OF TRAUMA**

- Provision of a safe environment
  - Home
  - Playground
  - Roads
- Education
  - Road safety awareness

**FIGURE 15-8.** Prevention of childhood fracture by prevention of trauma. What is needed is a broadly based public health approach to increasing the safety of children's environments in the home and playground and on the road. In addition, children should receive specific education on avoidance of road trauma.

**NONPHARMACOLOGIC FRACTURE PREVENTION IN ADULTS**

- Adequate diet
  - High calcium
  - Vitamin D
  - Low salt
  - Phytoestrogens
- Adequate exercise
  - Maintenance of bone mass
- Avoidance of toxins
  - Smoking
  - Excess alcohol
- Normal hormonal status
  - Estrogen
  - Testosterone

**FIGURE 15-9.** Nonpharmacologic fracture prevention in adults. Maintenance of peak bone mass can be considered under four headings: diet, exercise, skeletal toxins, and hormonal status. The effects of smoking on the skeleton have been assessed in observational studies. Smoking 20 cigarettes a day for 20 years reduced bone density at the spine by 9%, at the femoral neck by 6%, and at the femoral shaft by 6% [8]. The deleterious effects of alcohol are apparent only at high intakes, where other effects from poor nutrition and falls may be more important.

## Dietary Intervention for Bone Maintenance

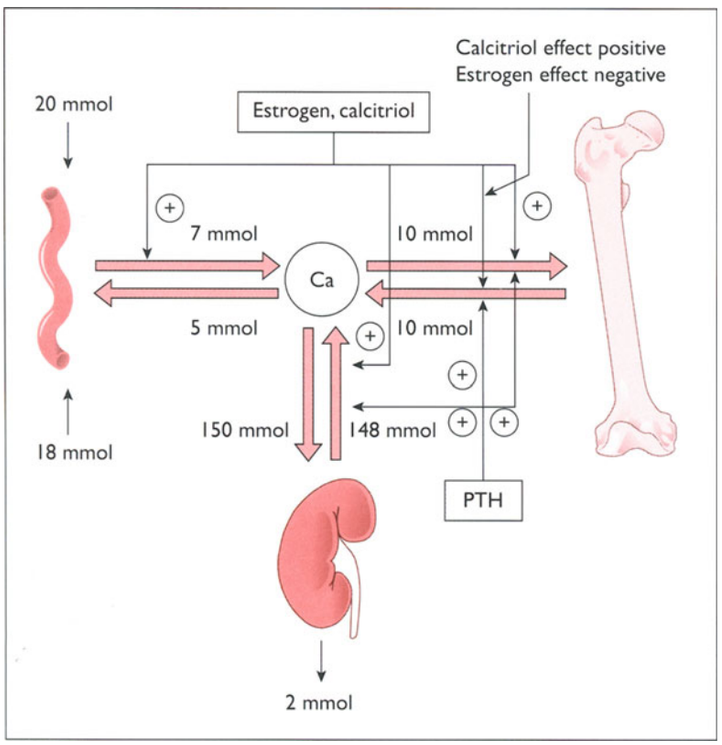



**FIGURE 15-10.** Regulation of organs involved in calcium transport. Dietary calcium supplementation can be considered in the context of calcium transport around the body. Calcium enters the bowel by ingestion of food and also by intestinal secretion of calcium. Net absorption into the extracellular space is from 2 to 4 mmol per day. This absorption is regulated by calcitriol and estrogen, both of which act to increase the absorbed fraction. Most of this absorbed calcium is excreted in the urine, although calcium also is lost in sweat. When the subject is in calcium balance, the amount of calcium entering the bone and leaving the bone is identical. In periods of dietary calcium deficiency, however, parathyroid hormone (PTH) rises. The rise in PTH induces an increase in bone resorption, an increase in calcium resorption from the urine, and an increase in calcitriol, which increase gut calcium absorption. If dietary calcium intake is low, more calcium leaves the bone than enters the bone to maintain extracellular calcium concentrations, resulting in osteoporosis. PTH stimulates new osteoid formation, ready for calcification at the time of an increase in dietary calcium.

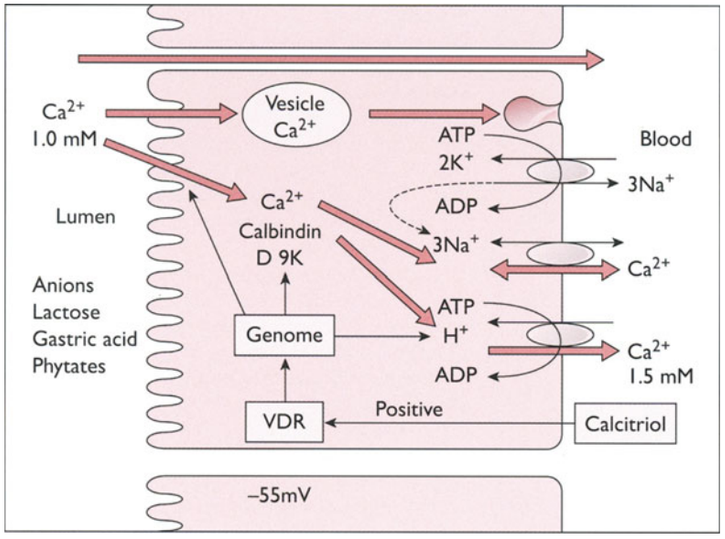



**FIGURE 15-11.** Factors associated with calcium transport across the bowel wall. The molecular biology of calcium absorption in the bowel is complex. In addition to paracellular absorption, which, although largely unregulated, is the major source of calcium absorption at high calcium loads, transcellular calcium absorption is strongly regulated. Vitamin D, in the form of its active metabolite, calcitriol, is the main regulator of gut calcium absorption, although there is some evidence that high concentrations of 25-hydroxyvitamin D may have an effect on calcium absorption. It is believed that genomic effects of calcitriol act to stimulate calcium absorption as well as calcium transport across the cell and calcium efflux at the basolateral membrane. This latter effect occurs by stimulation of both calcium ATPase and the sodium-calcium cotransporter [9]. Luminal factors affecting the physiochemical state of the calcium can influence absorption, especially the lack of gastric acid in the case of calcium carbonate [10,11]. Associated anions, such as citrate, appear to stimulate absorption. Dietary factors, such as phytates [12], impair absorption, whereas lactose, in the presence of lactase, stimulates absorption [13]. The molecular basis of these effects is uncertain but may be associated with paracellular absorption. ADP—adenosine diphosphate; ATP—adenosine triphosphate; VDR—vitamin D receptor.

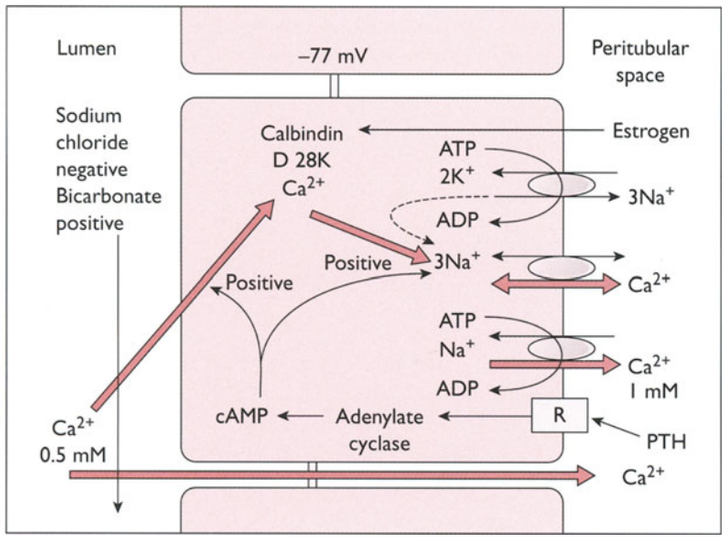



**FIGURE 15-12.** Factors regulating calcium transport via the distal tubule. Renal calcium transport also is vigorously regulated throughout the distal tubule. In the distal tubule, there is evidence that both parathyroid hormone (PTH) and estrogen stimulate calcium reabsorption via effects on the sodium-calcium exchanger and calcium ATPase [14,15]. The luminal concentration of other ions, including sodium chloride [16] and bicarbonate [17], also can affect calcium absorption, which occurs principally by the transcellular route. ADP—adenosine diphosphate; ATP—adenosine triphosphate; cAMP—cyclic adenosine monophosphate; PTH—parathyroid hormone.

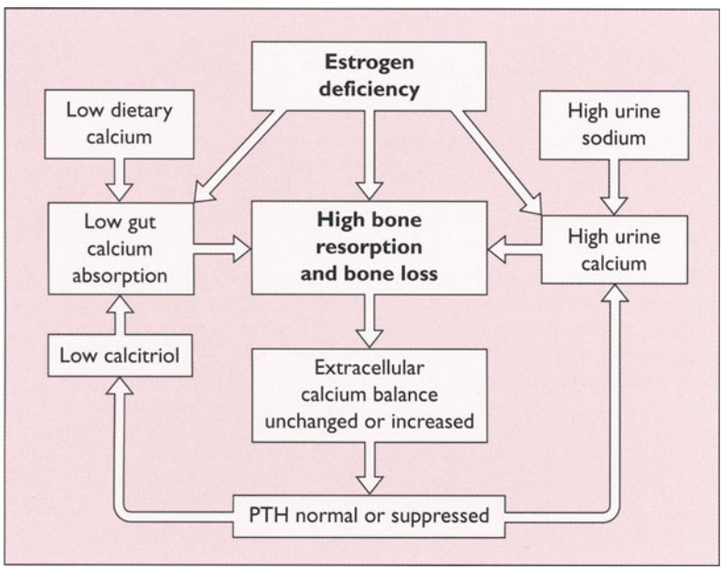



**FIGURE 15-13.** Role of dietary factors in early postmenopausal bone loss. Dietary calcium plays a small role in the bone loss that occurs close to the menopause. The principal cause of bone loss at this time is related to estrogen deficiency, which actually increases extracellular calcium concentrations, thereby suppressing renal calcium reabsorption and gut calcium absorption via effects on parathyroid hormone and calcitriol. Thus, the principal cause of the low gut calcium absorption and high renal calcium excretion at that time is the bone loss itself. In specific circumstances, a low dietary calcium or high urine sodium can exacerbate these losses and induce further bone loss [18]. PTH—parathyroid hormone.

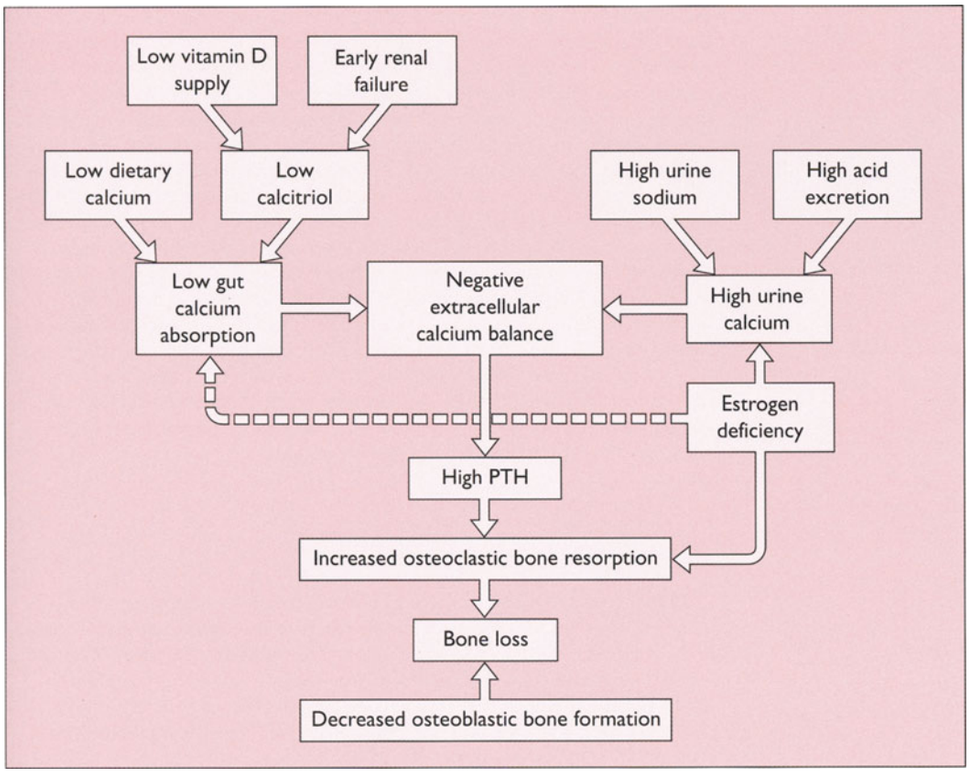



**FIGURE 15-14.** Dietary factors contributing to age-related bone loss. Age-related bone loss is dependent on a negative extracellular calcium balance inducing a high parathyroid hormone level. The negative extracellular balance is derived in approximately equal parts from a high urine calcium and a relatively low gut calcium concentration. The high urine calcium level is driven by estrogen deficiency and excessive ingestion of salt and high-acid foods.

Dietary calcium deficiency is exacerbated by impaired gut calcium absorption resulting from relatively low circulating levels of calcitriol and 25-hydroxyvitamin D. These levels are low because of early renal failure, preventing the formation of calcitriol, and a lack of vitamin D supply because of lack of exposure to sunlight. Estrogen deficiency also may play a role in the intrinsic defect in gut calcium absorption that occurs with aging.

The negative extracellular calcium balance induces a high parathyroid hormone level, which increases osteoclastic bone resorption. Increased bone turnover is associated with bone loss because of the age-related osteoblastic defect. PTH—parathyroid hormone.

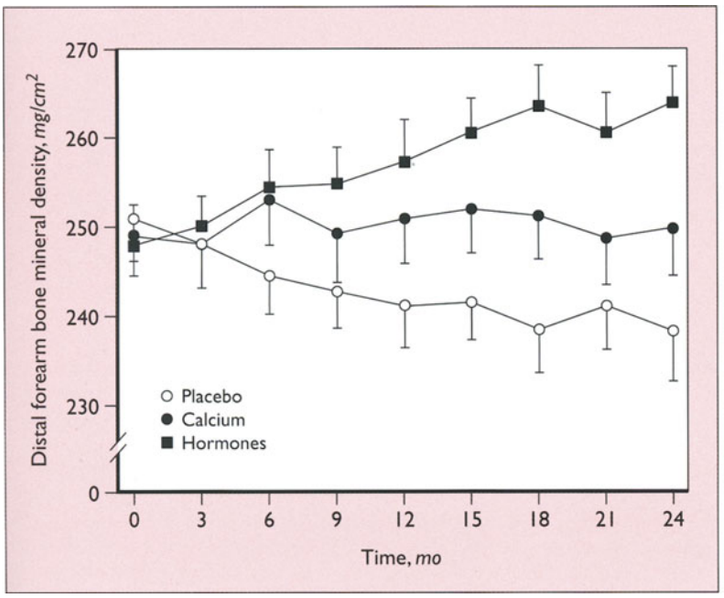



**FIGURE 15-15.** Calcium and estrogen replacement in postmenopausal women. In women less than 10 years past the menopause, calcium supplementation prevented forearm bone loss, but estrogen replacement increased bone mass slightly and was more effective than calcium alone [19]. This demonstrates that calcium is effective and that estrogen deficiency is associated, in part, with direct effects on calcium balance. *(Adapted from* Prince *et al.* [19].)

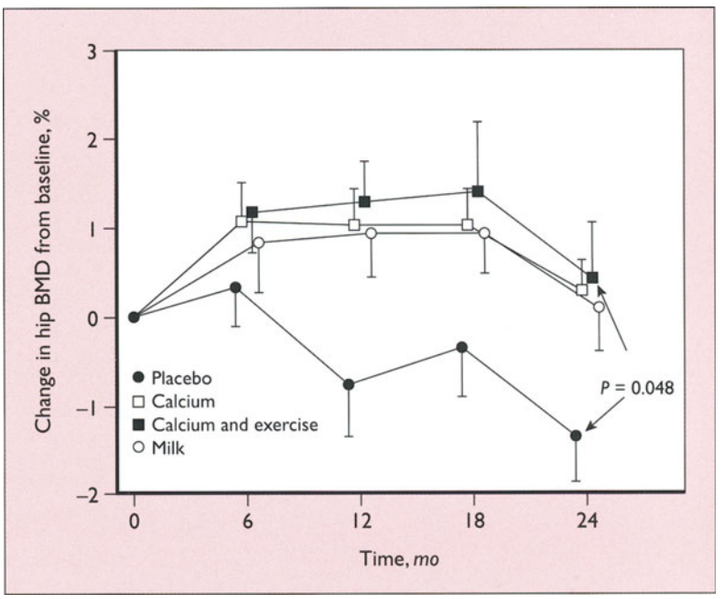
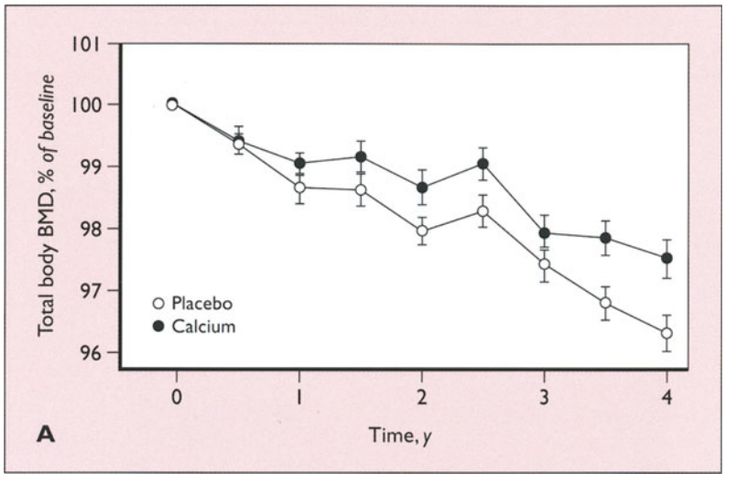



**FIGURE 15-16.** Effects of calcium supplementation and exercise on bone density at the hip. In women 15 years past the menopause, calcium supplementation of 1000 mg per day, either as a tablet or as milk powder, completely prevented hip bone loss over 2 years. Exercise offered little extra benefit [20]. BMD—bone mineral density. *(Adapted from* Prince *et al.* [20].)



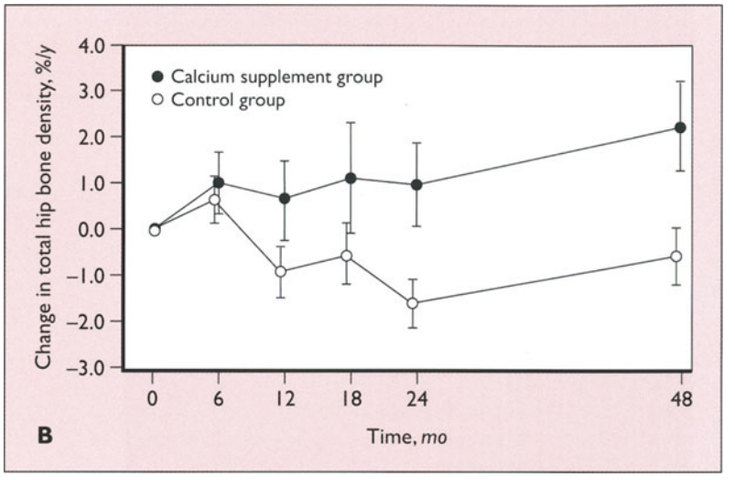




**FIGURE 15-17.** Effects of calcium supplementation on bone loss. Four years of calcium supplementation did not completely prevent total body bone density loss in women 10 years past the menopause (**A**). However, at the hip site, calcium supplementation was completely effective in stopping bone loss in women 15 years past the menopause (**B**) [19,20]. BMD—bone mineral density. (Part A *adapted from* Reid *et al.* [21]; Part B *adapted from* Devine *et al.* [22].)

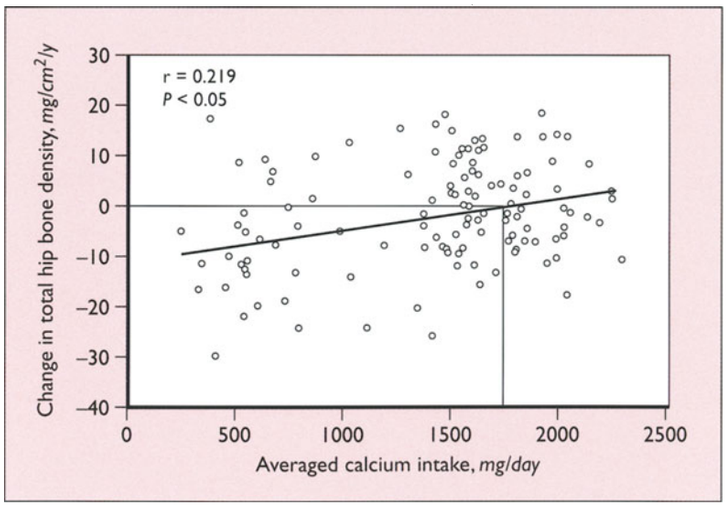



**FIGURE 15-18.** Effect of increasing calcium intake on bone loss in postmenopausal women. The dose of calcium required to prevent bone loss in postmenopausal women is uncertain. Data from 120 women followed prospectively over 2 years suggest that calcium intake to prevent bone loss at the hip should be more than 1500 mg per day. These values match the calcium requirement calculated from balance studies, in which the threshold is approximately 1200 mg per day [22]. *(Adapted from* Devine *et al.* [22].)

**CONTROLLED TRIALS OF CALCIUM: EFFECTS ON FRACTURE RATES**

| Study | Baseline Characteristics | Baseline Calcium Intake, mg/d | Intervention | Fracture Outcome in Control Group | Fracture Outcome in Treatment Group | Relative Risk | Absolute Risk Reduction (fractures per 100 patient years, 95% CI) | Number Needed to Treat |
|---|---|---|---|---|---|---|---|---|
| Chevalley *et al.* [23] | 11 males; 82 females; mean age, 73 y; 44% prevalent vertebral fractures | 650 | $CaCO_3$ or osseino complex 800 mg/d for 15 y | New vertebral fractures—10.7% | New vertebral fractures—7.4% | 0.69 | 33 (range, -7.8 to 14.3) | 30 |
| Reid *et al.* [21] | 135 women baseline; 78 women completed; mean age, 56 y; nonprevalent fractures | 700 | Calcium lactate gluconate1000 mg/d for 4 y | New fractures—18% | New fractures—5% | 0.3 | 31 (range, -0.4 to 6.5) | 32 |
| Recker *et al.* [24] | 92 women; mean age, 75 y; prevalent vertebral fractures | 450 | $CaCO_3$ 1200 mg/d for 4 y | New vertebral fractures—51% | New vertebral fractures—28% | 0.55 | 53 (range, 0.7 to 9.8) | 19 |
| Recker *et al.* [24] | 99 women; mean age, 73 y; nonprevalent vertebral fractures | 414 | $CaCO_3$ 1200 mg/d for 4 y | New vertebral fractures—21% | New vertebral fractures—28% | 1.33 | — | |

**FIGURE 15-19.** Effects of calcium supplementation on fracture rates. Three small randomized controlled trials of calcium supplementation have been undertaken. These show an absolute risk reduction of three to five fractures per hundred patient-years, or an absolute risk reduction ranging between 31% and 70% [21,23,24]. The Recker *et al.* [24] study showed no benefit in elderly women with nonprevalent vertebral fractures. The confidence intervals for these effects are large, and further studies are needed.

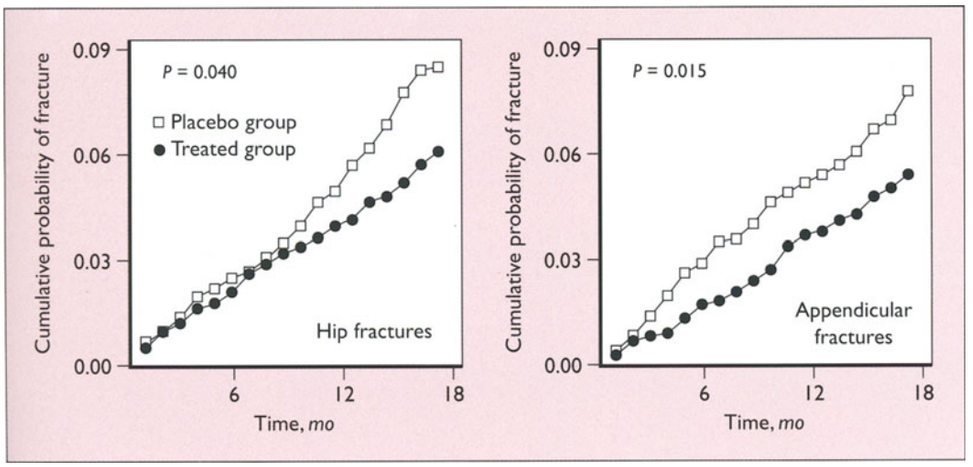



**FIGURE 15-20.** Effects of calcium plus vitamin D on fractures in elderly women. In women in institutional care (mean age, 84 years), calcium plus vitamin D not only prevented bone loss but also reduced hip fractures by 43% and nonvertebral fractures by 32% [25]. The participants in this trial apparently had inadequate intakes of both calcium and vitamin D before intervention started. (*Adapted from* Chapuy *et al.* [25].)

**CONTROLLED TRIALS OF CALCIUM AND VITAMIN D: EFFECTS ON FRACTURE RATES**

| Study | Baseline Characteristics | Baseline Calcium Intake, *mg/d* | Intervention, *per day* | Fracture Outcome in Control Group | Fracture Outcome in Treatment Group | Relative Risk (range) | Absolute Risk Reduction (fractures per 100 patient-years, 95% CI) | Number Needed to Treat |
|---|---|---|---|---|---|---|---|---|
| Chapuy *et al.* [25] | 2303 women Mean age, 84 y | 511 | $Ca_3(PO_4)_2$ 1200 mg, Vitamin D 800 IU for 3 y | Appendicular fractures—27.3% | Appendicular fractures—21.6% | 0.72 (0.6–0.84) | 1.9 (0.7–3.1) | 52 |
| Chapuy *et al.* [25] | 2303 women Mean age, 84 y | 511 | $Ca_3(PO_4)_2$ 1200 mg, Vitamin D 800 IU for 3 y | Hip fractures—15.8% | Hip fractures—11.6% | 0.73 (0.62–0.84) | 1.4 (0.4–2.3) | 71 |
| Dawson-Hughes *et al.* [26] | 176 men 213 women Mean age, 72 y | 700 | Calcium citrate malate 500 mg, Vitamin D 700 IU for 3 y | Appendicular fractures—12.8% | Appendicular fractures—5.9% | 0.5 (0.2–0.9) | 2.3 (0.4–4.2) | 43 |
| Dawson-Hughes *et al.* [26] | 213 women Mean age, 73 y | 700 | Calcium citrate malate 500 mg, Vitamin D 700 IU for 3 y | Appendicular fractures—19.6% | Appendicular fractures—11.6% | 0.6 (0.2–0.8) | 4.6 (0.8–8.4) | 22 |

**FIGURE 15-21.** Effects of calcium and vitamin D on fracture rates. Two larger intervention studies examining calcium plus vitamin D have been undertaken. The Chapuy *et al.* [25] study showed an absolute reduction of 1.4 hip fractures per hundred patients treated and 1.9 appendicular fractures per hundred patients treated. A smaller study in Boston studied both men and women. That study showed a 2.3% reduction in appendicular fractures [26,27]. Analysis of the data for the women alone showed a 4.6% reduction in fractures. These rates indicate that it is necessary to treat only between 20 and 50 individuals to prevent any appendicular fracture and 70 individuals to prevent hip fracture in 1 year.

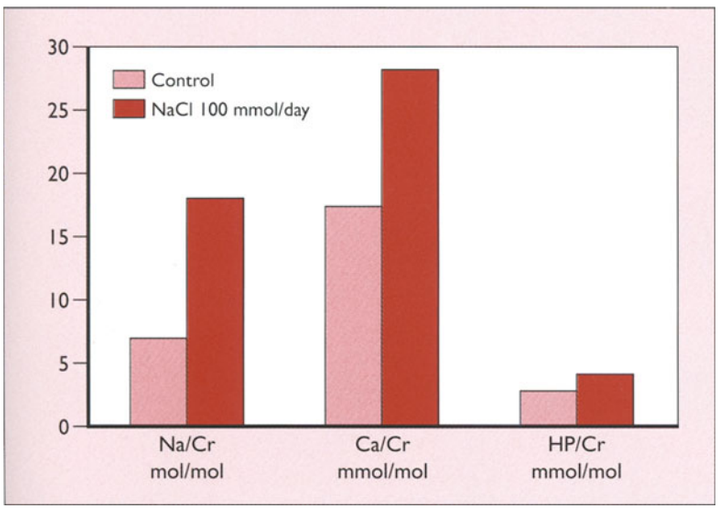



**FIGURE 15-22.** Effects of sodium loading on renal excretion. Increasing salt intake increases sodium excretion and calcium excretion in the kidney. It is also associated with an increase in bone resorption, as measured by the hydroxyproline-creatinine ratio [28]. Cr—creatinine; HP—hydroxyproline. *(Adapted from* Goulding [28].)

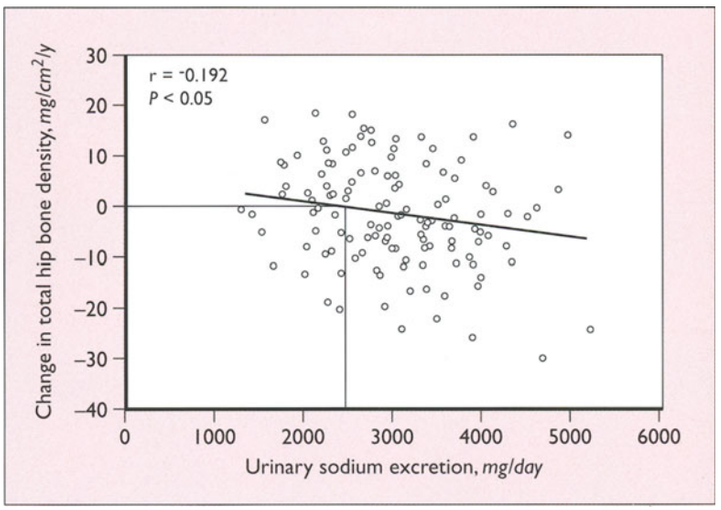



**FIGURE 15-23.** Effects of increasing sodium intake on bone loss at the hip in postmenopausal women. In postmenopausal women, the higher the sodium excretion over 2 years, the greater the bone lost at the hip [29]. *(Adapted from* Devine *et al.* [29].)

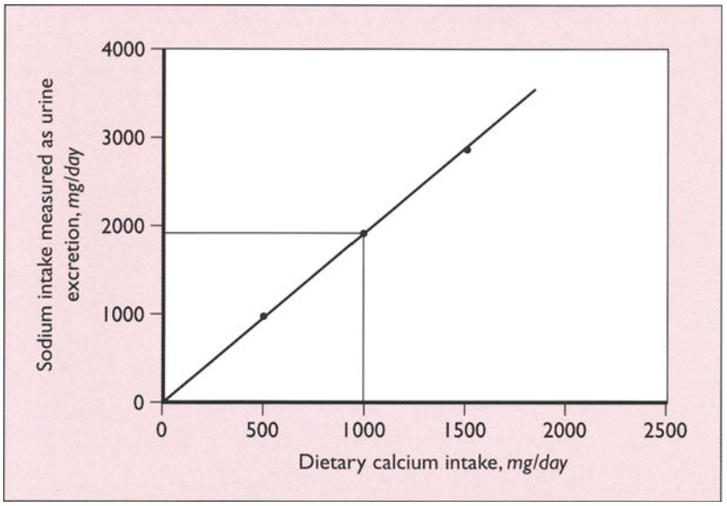



**FIGURE 15-24.** Determinants of hip bone density. Two determinants of hip bone density are dietary calcium intake and salt intake, as measured by sodium excretion. The higher the dietary calcium intake, the lower the bone loss. The higher the salt intake, the higher the bone loss. It is, therefore, possible to balance intakes of these two nutrients. The data show that with a dietary calcium intake of 1000 mg per day, provided that sodium intake is less than 2000 mg, no bone loss in the hip will occur [29]. *(Adapted from* Devine *et al.* [29].)

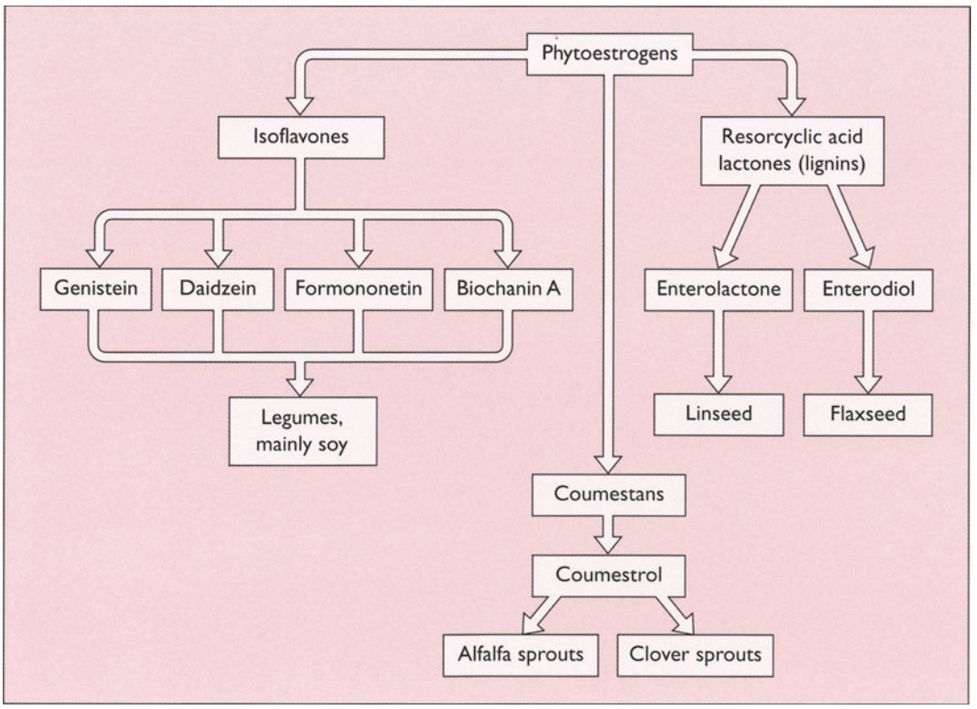



**FIGURE 15-25.** Types and sources of phytoestrogens. The three major groups of phytoestrogens are isoflavones, coumestans, and resorcyclic acid lactones. In terms of human disease, soy has been the most extensively studied, containing mostly isoflavones, although it also contains a small amount of coumestrol. The coumestans are more potent ligands for the estrogen receptor, however.

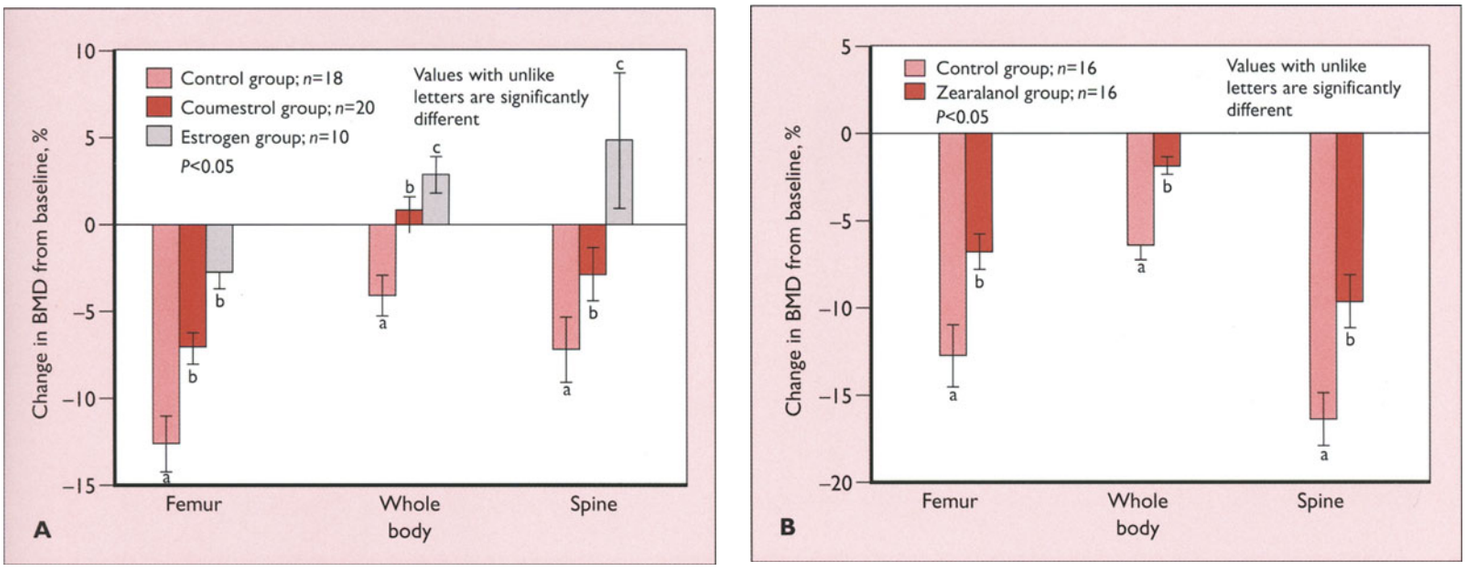



**FIGURE 15-26.** Effects of phytoestrogens on bone density in aging rats. Studies in the aged rat model of postmenopausal osteoporosis indicate that coumestrol significantly reduces bone loss at the spine and hip and completely prevents bone loss in the whole body (**A**). Another phytoestrogen, zearalanol, also demonstrates efficacy in reducing bone loss after oophorectomy (**B**). Dose calculations suggest that consumption of 350 g of alfalfa sprouts per week may provide enough coumestrol to provide beneficial effects on bone in humans [30]. *(Adapted from* Draper *et al.* [30].)

## Role of Activity and Exercise

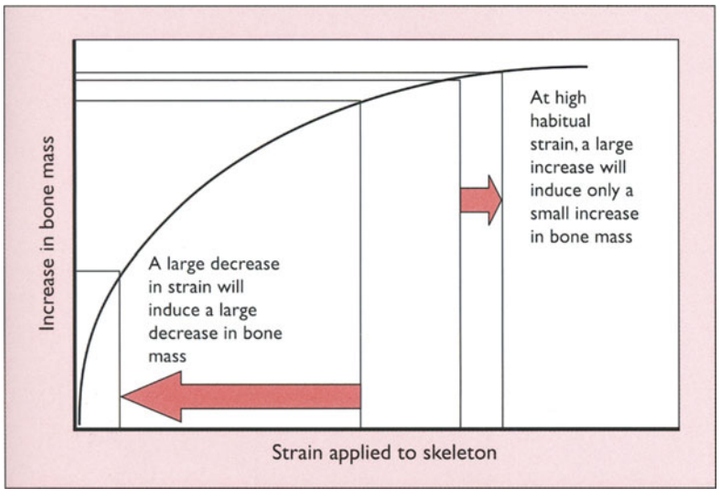



**FIGURE 15-27.** Relation between induced strain and osteogenic response. Strain relationships applied to the skeleton show very significant effects on periosteal bone formation in animal models of stress-strain relationship. Studies in healthy adults show small effects of increasing stress-strain relationships to increase bone density at the site to which the strain has been applied. Similarly, studies of immobilization resulting from hemiplegia or stroke show dramatic reductions in bone density. Studies that show a significant increase in bone density with exercise in patients previously immobilized have not yet been performed.

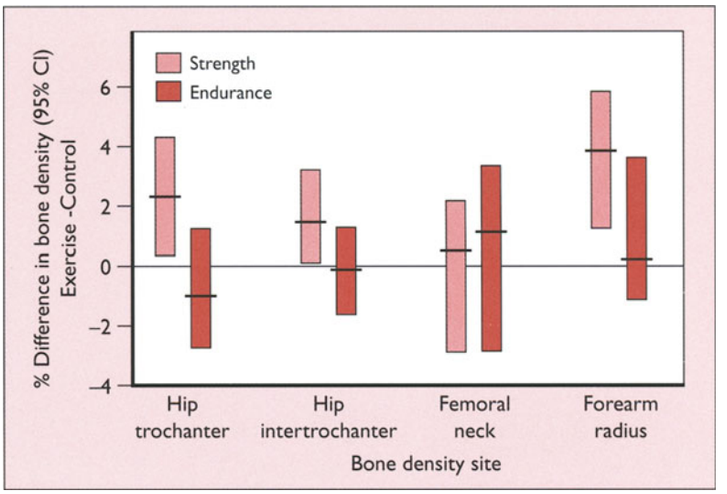



**FIGURE 15-28.** Effects of exercise on bone density. The effects of exercise on bone density depend on the site of maximal change in the stress-strain relationship. Adjacent sites in the hip can show significant effects or no effects. The figure shows that the strength regimen, which included weight training, significantly increased the bone density at the trochanter and intertrochanter site, but had no effect at the femoral neck site. The endurance regimen, which did not increase stress-strain relationships as much as did the weight lifting regimen, showed no overall effect on bone density [31]. *(Adapted from* Kerr *et al.* [31].)

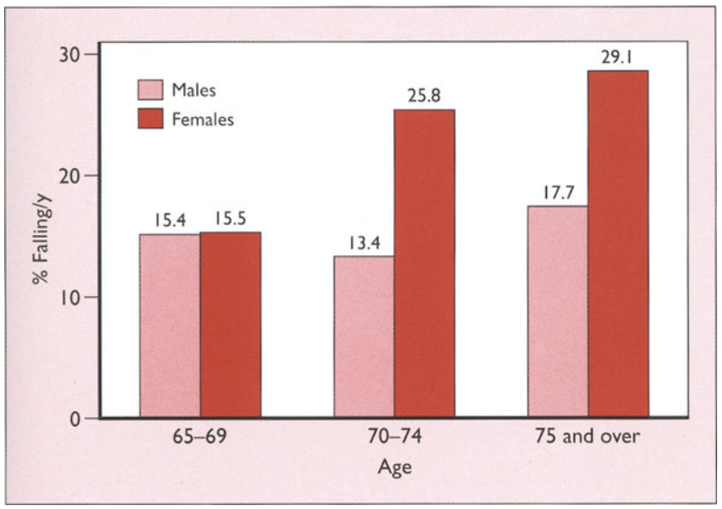



**FIGURE 15-29.** Incidence of falls in elderly men and women. Prevention of falls is a potentially important public health approach to the prevention of osteoporotic fractures. The incidence of falls is highly age dependent, especially in women [32]. (*Adapted from* Australian Bureau of Statistics [32].)

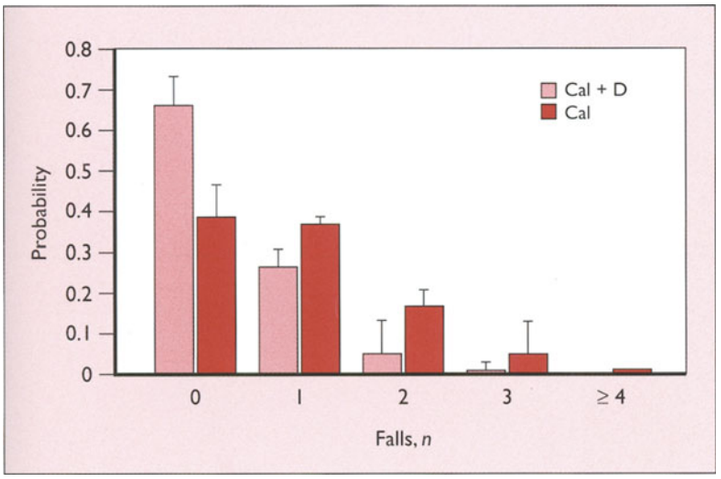
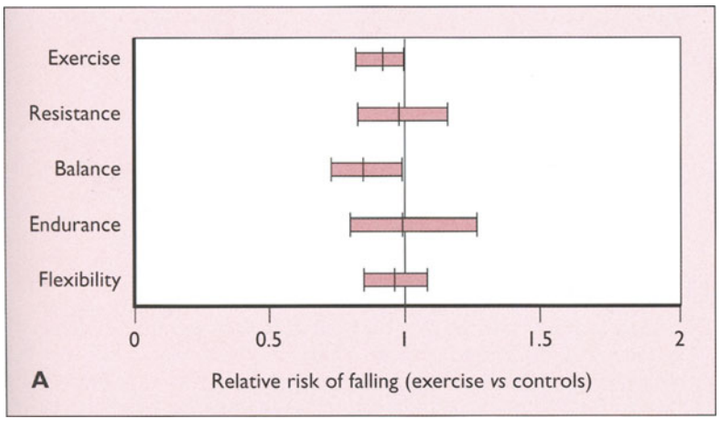



**FIGURE 15-30.** The effects of vitamin D and calcium supplementation on falls. Vitamin D deficiency can cause muscle weakness, and vitamin D supplementation can increase muscle strength. Recently, Bischoff *et al.* [33] showed that vitamin D and calcium supplementation in a group of older women with vitamin D deficiency improved muscle performance and reduced the risk of falling. The figure shows that during the 3-month treatment period, those who received vitamin D (800 IU/d) and calcium (1200 mg/d) fell less often. The results shown were adjusted for previous falls, age, and baseline vitamin D levels (these factors also affect fall risk). The results suggest that vitamin D and calcium nutrition may influence fracture risk not only by affecting bone directly but also by reducing the risk of falls. This emphasizes the need to ensure adequate vitamin D and calcium nutrition in people at risk for fractures, especially the elderly, who are at high risk for nutritional deficiencies. (*Adapted from* Bischoff *et al.* [33].)



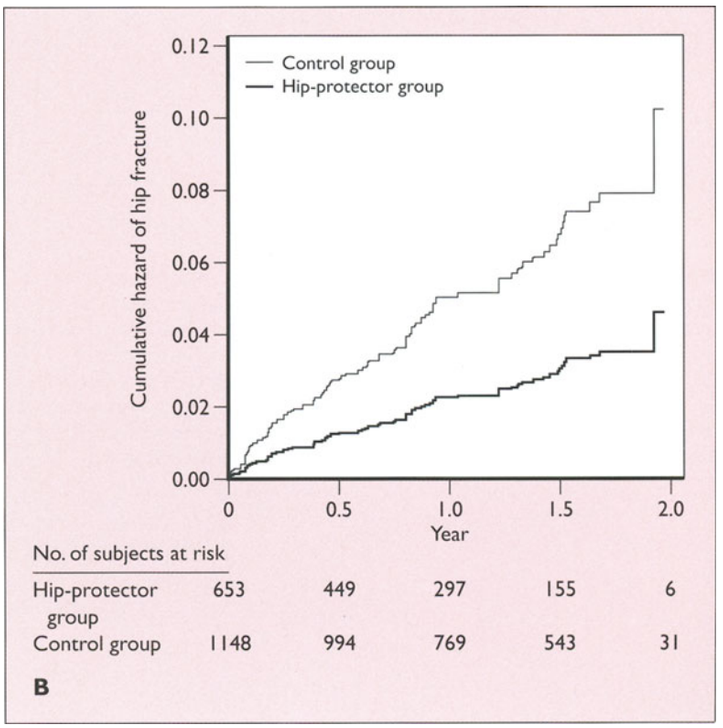




**FIGURE 15-31.** Prevention of trauma resulting from falls. Preliminary studies of exercise regimens show that some interventions can significantly reduce falls, although this has not yet been shown to prevent fractures. **A**, The effects of various types of exercise regimens on the relative time to first fall. Regimens involving balance and exercise appear to be better than those involving resistance weight training and flexibility [34]. Another approach to fracture prevention is to apply hip protectors over the greater trochanter to cushion the fall. **B**, The relative risk of hip fracture in subjects randomized to wear hip protectors or not. In this study, a significant reduction in hip fractures in subjects wearing hip protectors is shown [35]. (Part A *adapted from* Province *et al.* [34].)

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# 16

# BISPHOSPHONATE THERAPY FOR OSTEOPOROSIS

*Nelson B. Watts*

Bisphosphonate treatment of osteoporosis began with off-label use of etidronate in the 1980s. Alendronate (1995) and risedronate (1999) are approved by the US Food and Drug Administration (FDA) for prevention and treatment of postmenopausal osteoporosis and for patients with osteoporosis due to glucocorticoid treatment. These compounds increase bone mineral density and reduce the risk of fractures of the vertebrae, hips, and other nonvertebral sites. The body of evidence for both safety and efficacy of bisphosphonate treatment of osteoporosis is stronger than for any other agent. Bisphosphonates are safe and well tolerated and represent the agents of choice for most patients with osteoporosis.

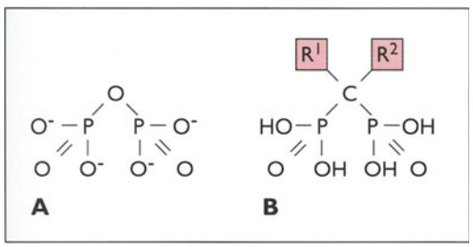


**FIGURE 16-1.** General structure of pyrophosphate (**A**) and bisphosphonates (**B**). Bisphosphonates are analogues of pyrophosphates. Pyrophosphates are ubiquitous compounds characterized by two phosphonic acid groups bound to a central oxygen molecule. The phosphate-oxygen bonds undergo rapid enzymatic degradation. Bisphosphonates consist of two phosphonic acids linked to a carbon, with two side chains ($R^1$ and $R^2$) that determine the avidity of binding to bone, antiresorptive potency, and side effects. (*Adapted from* Watts [1].)

**CHARACTERISTICS OF BISPHOSPHONATES**

- Effective orally or intravenously
- Absorption is poor when given by mouth and completely blocked by divalent cations
- Bind avidly to hydroxyapatite crystals on bone surfaces
- No systemic metabolism
- Excreted by the kidney
- Long retention in skeleton

**FIGURE 16-2.** Characteristics of bisphosphonates. Bisphosphonates can be administered orally or intravenously, but they are poorly absorbed when given by mouth. Under ideal circumstances, only about 1% of an oral dose is absorbed; absorption is completely blocked if the drug is taken with calcium, magnesium, or other divalent cations. Bisphosphonates bind avidly to hydroxyapatite crystals on bone surfaces. Between 20% and 50% is adsorbed on bone, and the rest is excreted in urine over the next 12 to 24 hours. There is no systemic metabolism. Although the drug remains in bone for years, after remodeling is complete it is buried in bone and is no longer pharmacologically active. Bisphosphonates have little or no long-term toxicity. The main side effects are gastrointestinal (esophageal irritation), most likely with nitrogen-containing bisphosphonates given orally, and acute-phase reactions, hypocalcemia, and acute renal failure when given intravenously. Etidronate, given continuously and in high doses, may impair bone mineralization, but this is rarely seen with the doses of other bisphosphonates used to treat osteoporosis.

**MECHANISMS OF ANTIRESORPTIVE ACTION OF BISPHOSPHONATES**

- Reduce activity of individual osteoclasts
  - Inhibit lactate production
  - Inhibit lysosomal enzymes
- Reduce activation frequency
  - Inhibit recruitment of osteoclast precursors
  - Inhibit differentiation of osteoclast precursors
- Accelerate osteoclast apoptosis

**FIGURE 16-3.** Mechanisms of antiresorptive action of bisphosphonates. After being adsorbed onto hydroxyapatite crystals at sites of active bone remodeling, bisphosphonates decrease bone turnover through several different actions: 1) they reduce the activity of individual osteoclasts by inhibiting production of lactate and lysosomal enzymes; 2) they reduce activation frequency by inhibiting recruitment and differentiation of osteoclast precursors, and 3) they accelerate osteoclast apoptosis (programmed cell death).

**TYPES OF BISPHOSPHONATES**

- Non–nitrogen-containing
  - Etidronate
  - Clodronate
  - Tiludronate
- Nitrogen-containing
  - Pamidronate
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate

**FIGURE 16-4.** Different types of bisphosphonates. Altering the $R^2$ side chain on bisphosphonates changes the antiresorptive potency. The antiresorptive potency differs 10 to 10,000 fold between compounds based on *in vitro* testing; *in vivo*, the difference in potency between compounds is less. Early bisphosphonates in clinical use (etidronate, clodronate, and tiludronate) are rather simple compounds. Newer bisphosphonates (pamidronate, alendronate, risedronate, ibandronate, and zoledronate) have greater antiresorptive potency than the older compounds, in part because they contain at least one nitrogen in the $R^2$ side chain. Although sometimes classified in "generations," most authorities now classify bisphosphonates on the basis of whether or not a nitrogen is contained in the $R^2$ side chain.

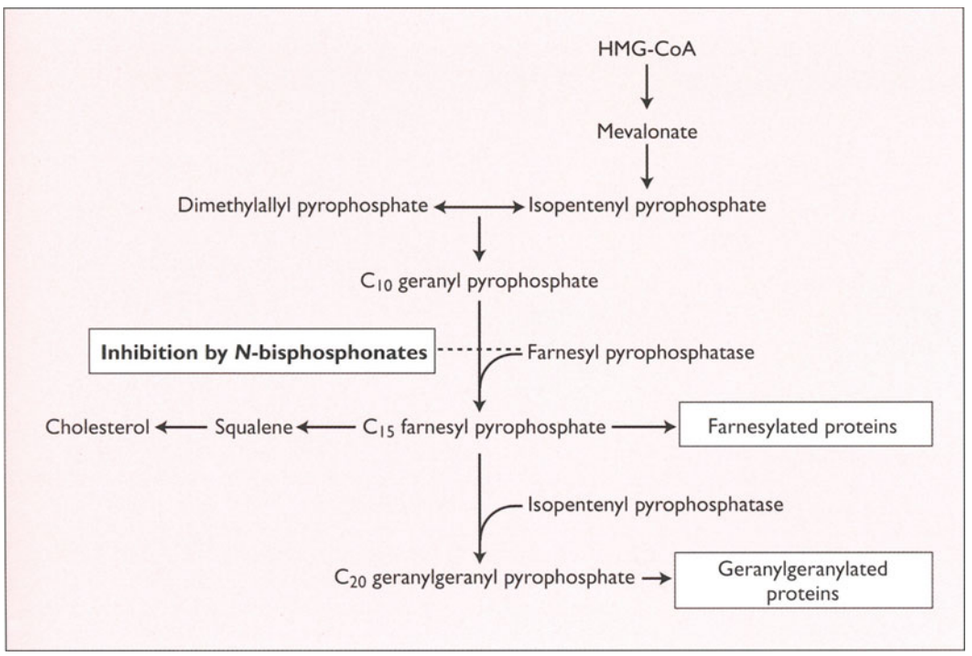


**FIGURE 16-5.** Intracellular mechanism of action of nitrogen-containing bisphosphonates. Protein prenelation (addition of 15- and 20-carbon lipid side chains) is essential for the optimal action of a number of GTPases that are critical for cellular function and integrity. Nitrogen-containing bisphosphonates interfere with protein prenelation by inhibiting the action of farnesyl pyrophosphate synthase, an enzyme in the mevalonate pathway. The end result of the decreased action of these GTPases is apoptosis (programmed cell death) of osteoclasts and, therefore, reduced bone resorption [2]. Non–nitrogen-containing bisphosphonates exert their action by causing the accumulation of toxic analogues of adenosine triphosphate (ATP) within cells (*not shown*).

**POTENTIAL MEDICAL USES FOR BISPHOSPHONATES**

- Osteoporosis
- Hypercalcemia
- Paget's disease
- Fibrous dysplasia
- Osteogenesis imperfecta
- Multiple myeloma
- Bone metastases
- Myositis ossificans
- Heterotopic ossification
- Periodontal disease
- Neuropathic arthropathy (Charcot's joint)

**FIGURE 16-6.** Potential medical uses for bisphosphonates. Bisphosphonates appear to be beneficial in almost any condition characterized by increased bone remodeling, including osteoporosis, hypercalcemia, and Paget's disease.

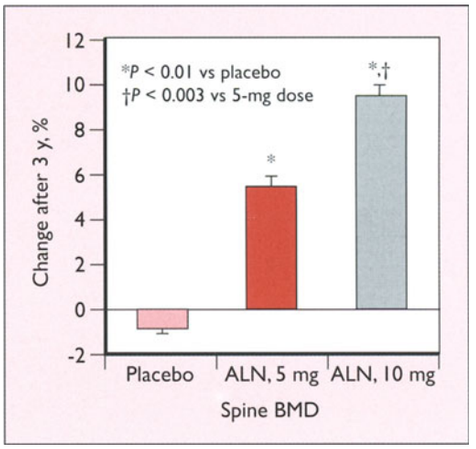


**FIGURE 16-7.** Effect of bisphosphonates on spine bone mineral density (BMD). In women with postmenopausal osteoporosis, bisphosphonates increase BMD in a dose-dependent manner. In this 3-year study of 478 women with postmenopausal osteoporosis, the optimal dose of alendronate (ALN) for increasing bone density in the spine was 10 mg daily. (*Data from* Tucci *et al.* [3].)

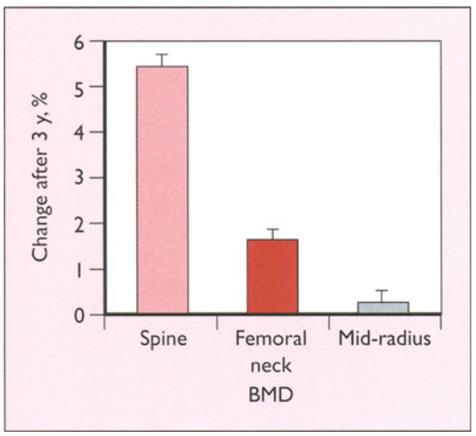


**FIGURE 16-8.** Effects of bisphosphonates on bone mineral density (BMD) at different skeletal sites. Although treatment with bisphosphonates produces significant gains in BMD in the spine in women with postmenopausal osteoporosis, the effect of treatment is less at the hip, and negligible at the forearm, as shown in this 3-year study of 2458 women with osteoporosis receiving risedronate, 5 mg daily [4].

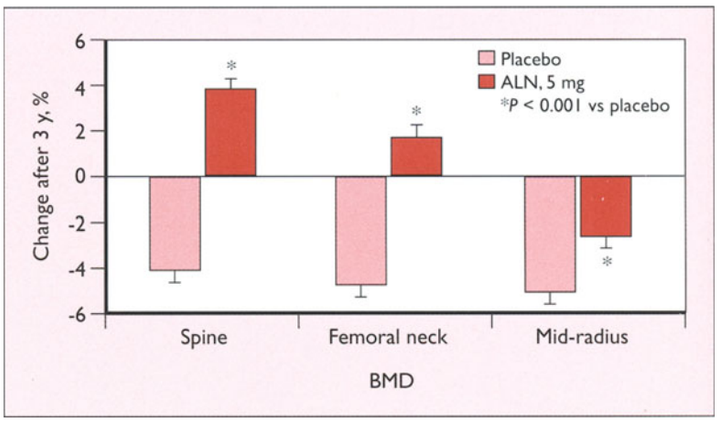


**FIGURE 16-9.** Bisphosphonates prevent loss of bone mineral density (BMD) in recently menopausal women. Bisphosphonates have been shown to prevent or reduce the accelerated bone loss that occurs with menopause, as illustrated in this study of 1174 women in early menopause treated with alendronate (ALN), 5 mg daily, or placebo [5].

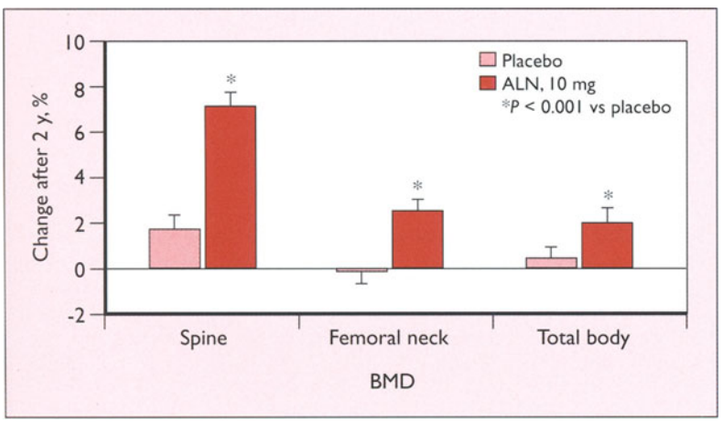


**FIGURE 16-10.** Bisphosphonates increase bone mineral density (BMD) in men with osteoporosis. In this 2-year trial of 241 men with osteoporosis, alendronate (ALN), 10 mg daily, produced gains in BMD in the spine and hip similar to those seen in alendronate-treated women with postmenopausal osteoporosis [6].

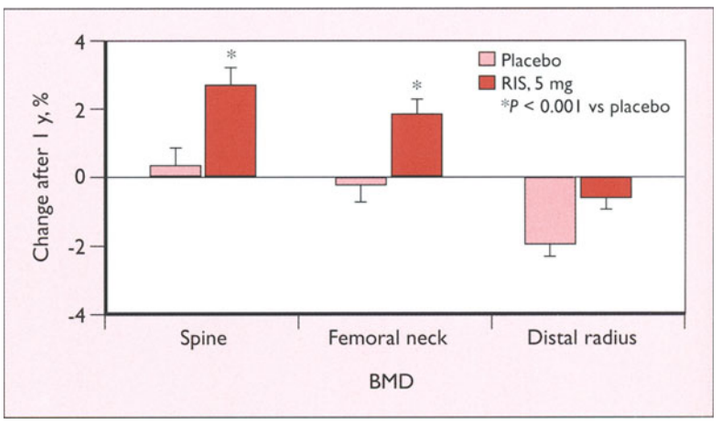


**FIGURE 16-11.** Bisphosphonates have positive effects on bone mineral density (BMD) in patients receiving corticosteroid therapy. Bisphosphonates prevent bone loss in patients beginning corticosteroid therapy, and increase BMD in patients who have been on long-term corticosteroid therapy. In this 12-month study of 290 men and women who had received prednisone, 7.5 mg daily or more, for an average of about 5 years, treatment with risedronate (RIS), 5 mg daily, resulted in significantly better BMD in the spine and hip compared with placebo [7].

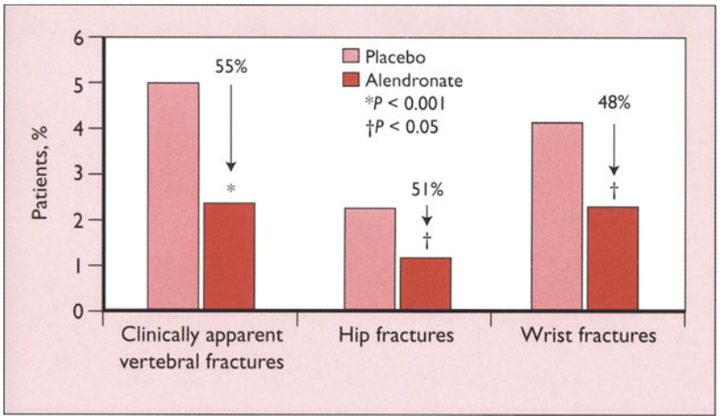


**FIGURE 16-12.** Bisphosphonates reduce fracture risk in women with postmenopausal osteoporosis. The main value of any treatment for osteoporosis is reduction in fracture risk. The first prospective, randomized, double-blind, placebo-controlled trial to demonstrate an antifracture effect with any agent was the Fracture Intervention Trial (FIT), a 3-year study of 2027 women with postmenopausal osteoporosis (all with prevalent vertebral fractures) who received either alendronate (5 mg daily for 2 years, then 10 mg daily) or placebo. Rates of vertebral fractures, hip fractures, and wrist fractures were significantly decreased with alendronate treatment compared with placebo [8]. Of interest, in this study, fracture rates were reduced to a similar degree at these three skeletal sites, despite different effects on bone density at these sites (Fig. 16-8).

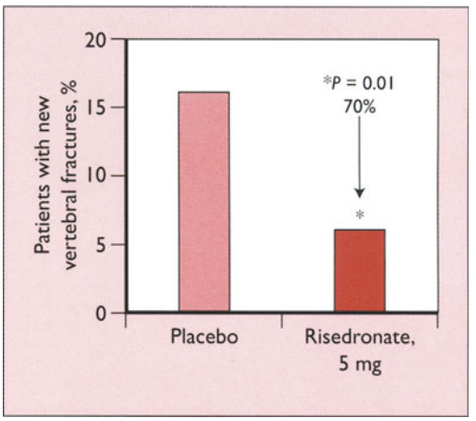


**FIGURE 16-13.** Bisphosphonates have been shown to reduce fracture risk in corticosteroid-treated patients. Pooled data from two studies involving 518 men and women receiving moderate to high doses of corticosteroids showed that risedronate, 5 mg daily, significantly reduced the percentage of patients with new vertebral fractures (vs placebo) after 12 months of treatment [9].

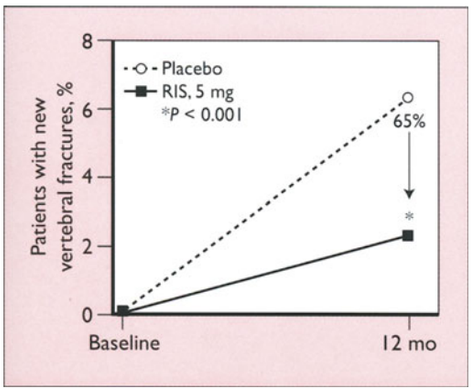


**FIGURE 16-14.** Bisphosphonates reduce the risk of fractures rapidly. Bisphosphonates have been shown to reduce the risk of clinical and radiographic vertebral fractures quickly. In this study, radiographic vertebral fractures assessed at 1 year were significantly reduced with risedronate (RIS), 5 mg daily, compared with placebo [4].

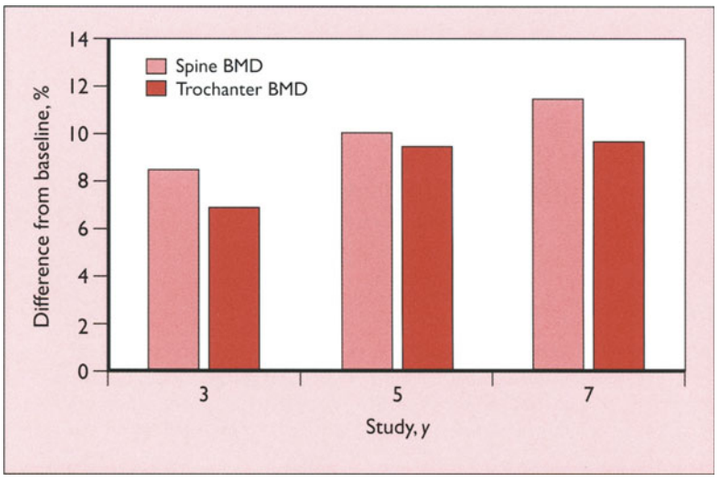


**FIGURE 16-15.** Bone mineral density (BMD) continues to increase through at least seven years' treatment with bisphosphonates. Although the most rapid gain in BMD with bisphosphonate treatment occurs in the first year or two, continued alendronate treatment through 7 years produced continuing gains in BMD [10].

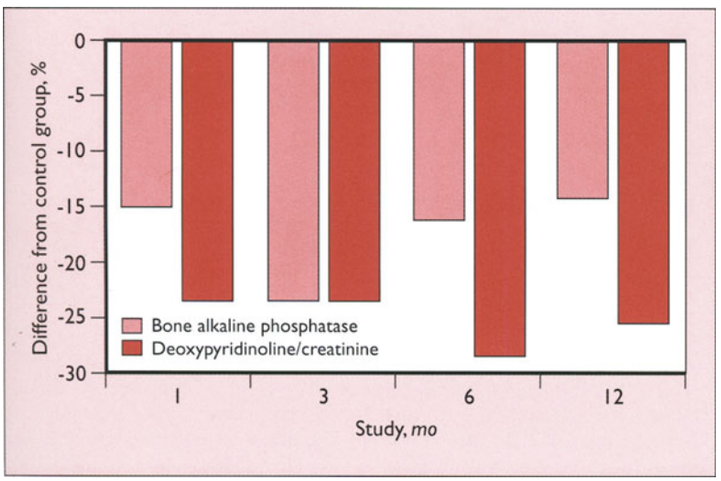


**FIGURE 16-16.** Effects of bisphosphonates on bone turnover markers. Bisphosphonates exert an antiresorptive effect that is reflected in a rapid reduction in bone turnover markers, such as bone alkaline phosphatase and deoxypyridinoline, as shown in this study during 12 months' treatment with risedronate, 5 mg daily [4]. The reduction in bone turnover markers is rapid (usually maximal after 3 to 6 months of treatment) and maintained for as long as treatment is continued. The timing of maximal reduction in bone turnover markers is concordant with the early fracture reduction. The degree of reduction in bone turnover correlates better with fracture reduction than does change in bone mineral density.

**PROPER DOSING OF ALENDRONATE**

| Instruction | Reason |
|---|---|
| Take on an empty stomach first thing in the morning, with water only, and nothing else for 30 minutes | Avoids binding with divalent cations to ensure adequate absorption |
| Take with 8 ounces of water | Minimizes risk of the tablet lodging in the esophagus |
| Remain upright until food or calcium is consumed to bind the drug | Minimizes the risk of reflux of the drug into the esophagus |

**FIGURE 16-17.** Proper oral administration of bisphosphonates. Bisphosphonates are poorly absorbed when given by mouth, and must be taken on an empty stomach, with water, but nothing else for at least 30 minutes. Alendronate may irritate the esophagus, so the tablet should be washed down with water (to avoid sticking) and the patient should remain upright (seated or standing) until they have taken some food or calcium to bind the drug. Bisphosphonates should not be given to patients with active upper gastrointestinal disease and should be stopped if upper gastrointestinal symptoms develop.

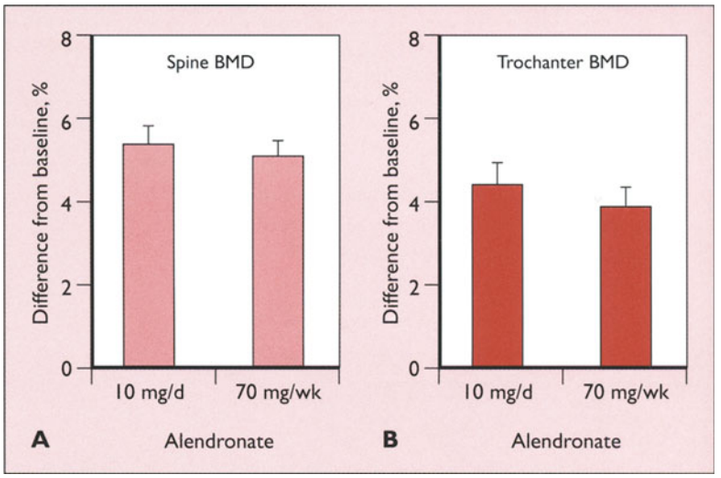


**FIGURE 16-18. A** and **B**, Oral bisphosphonates can be given once weekly. The daily dosing routine with bisphosphonates may seem confining. A 12-month study showed essentially equivalent effects of alendronate, 70 mg once weekly, compared with alendronate, 10 mg daily, on bone mineral density (BMD) and on bone turnover markers [11]. Similar results have been shown for weekly versus daily dosing with risedronate [12].

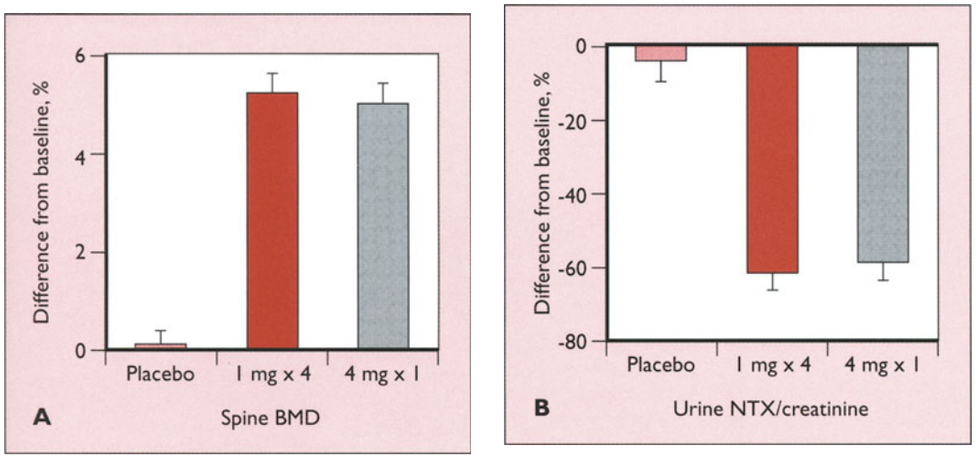


**FIGURE 16-19. A** and **B**, Bisphosphonates are effective when given intravenously. Some patients cannot tolerate oral bisphosphonates, and others may not absorb the drug when it is given by mouth. Small studies suggest that intravenous pamidronate given every third month will increase bone mineral density (BMD) and decrease bone turnover markers. A recent study of 351 women showed that zoledronate (zoledronic acid) given as a single 4-mg dose compared with zoledronate 1 mg every third month produced similar effects on bone mineral density and had a similar and sustained effect on bone turnover over 12 months [13]. Several large studies are underway to determine whether intravenous zoledronate therapy will reduce fracture risk. NTX—N-telopeptides of type II collagen.

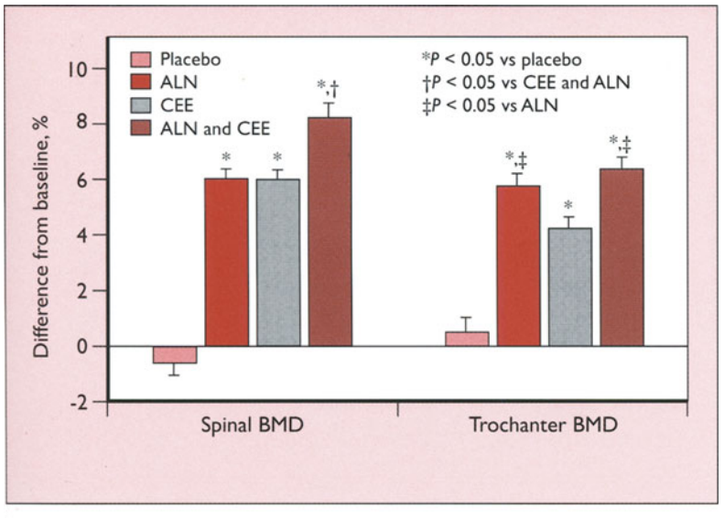


**FIGURE 16-20.** Combination therapy. Combining two antiresorptive drugs has been shown to produce slightly additive effects on bone mineral density (BMD), as shown in this study of 425 women randomized to receive placebo, alendronate (ALN) 10 mg daily, conjugated estrogen (CEE) 0.625 mg daily, or a combination of alendronate plus estrogen [14]. Similar effects have been shown for alendronate plus raloxifene (Evista; Lilly, Indianapolis, IN) and risedronate plus estrogen. However, the addition of a second medication increases the cost and the potential for side effects, and has not been shown to produce a greater reduction in fracture than that with the use of a single agent, and therefore cannot be recommended [15].

**BISPHOSPHONATES CURRENTLY APPROVED BY THE FDA FOR USE IN OSTEOPOROSIS**

Alendronate
- Prevention and treatment of postmenopausal osteoporosis
- Treatment of glucocorticoid-induced osteoporosis
- Treatment of osteoporosis in men

Risedronate
- Prevention and treatment of postmenopausal osteoporosis
- Prevention and treatment of glucocorticoid-induced osteoporosis

**FIGURE 16-21.** Bisphosphonates currently approved by the US Food and Drug Administration (FDA) for use in osteoporosis. Only two bisphosphonates, alendronate and risedronate, are currently approved by the FDA for use in osteoporosis. Etidronate, tiludronate, pamidronate, and zoledronate are marketed in the United States for other indications and are sometimes used "off label" for treatment of osteoporosis. Ibandronate and zoledronate are actively being developed for osteoporosis indications.

Of all the agents currently available, bisphosphonates have been studied most extensively. Safety appears excellent. Tolerability of once-weekly dosing is good. Although nasal calcitonin and raloxifene have been shown to reduce the risk of vertebral fractures, they have not been shown to have an effect on hip or other nonvertebral fractures. Teriparatide (parathyroid hormone), recently approved, has been shown to reduce the risk of nonvertebral fractures, but not to reduce the risk of hip fracture. On balance, bisphosphonates remain the agent of choice for treatment of most patients who have osteoporosis.

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# 17

# BONE ANABOLIC AGENTS

*Clifford J. Rosen*

Bone remodeling is a complex but coupled process in which old bone is resorbed, followed by the formation of new bone. Ten percent of the human skeleton is remodeled per year. Osteoporosis is a disorder of bone remodeling characterized by uncoupling of resorption from formation. The net result is a loss of bone mass. Pharmacologic agents can restore bone mass by inhibiting bone resorption or stimulating new bone formation; antiresorptive agents suppress osteoclast-mediated dissolution more than bone formation, resulting in a secondary increase in bone mineral density (BMD). This alters the remodeling sequence and strengthens bone by reducing microperforations. In turn, osteoporotic fractures of the hip and spine are reduced. At the present time, virtually all drugs, except one, that are approved by the US Food and Drug Administration (FDA) for the treatment of established osteoporosis act to inhibit bone resorption. These include calcitonin, estrogen, raloxifene (Evista; Lilly, Indianapolis, IN), risedronate, and alendronate. Other bisphosphonates, such as etidronate and pamidronate, are also antiresorptives and are available "off label" even though not officially approved by the FDA. All these agents, as well as calcium and vitamin D supplementation, inhibit bone resorption, although their mechanisms of action differ considerably. Increases in bone mass that result from antiresorptive therapy range from 1% to 8% over 5 years, before a new steady state in the skeleton is reached. Some agents, such as alendronate, show increases in spine BMD for as long as 8 years after treatment. Despite this positive effect, there still are lingering concerns about the long-term safety of the bisphosphonates with regard to the skeleton, particularly with respect to persistent suppression of bone turnover. Hence, there has been a push for peptides and growth factors that work on osteoblasts and stimulate bone formation—*anabolic agents*.

Anabolic agents for the skeleton, by definition, are compounds that directly enhance BMD. Although more than 20 years ago parathyroid hormone (PTH) extract was given experimentally to a few women with osteoporosis, sodium fluoride (NaF) was the first anabolic drug administered to patients both in clinical trials and "off label." Despite more than two decades of clinical trials, NaF is still considered experimental, whereas PTH (1-34) has recently been approved for the treatment of severe postmenopausal osteoporosis. The ambiguity surrounding NaF relates, in part, to concerns about the quality of new bone formed with this therapy. In at least one large multicenter trial, NaF showed a substantial increase in bone density over 3 years, but there were more nonvertebral fractures in the treated women than in the placebo group [1]. Hence, NaF may increase BMD, especially in the spine, but at the expense of bone strength. By contrast, PTH increases spine and hip BMD but decreases vertebral and nonvertebral fractures by at least 50% [2].

Early in the 1980s, a whole generation of recombinant peptides were produced for clinical trials of various disorders, including osteoporosis. As noted in Figure 17-1, there is only one approved anabolic treatment for osteoporosis, PTH (1-34) [2,3]. This drug must be administered daily as a subcutaneous injection. The mechanism of its action is still not defined, although it is clear that PTH, when administered continuously, does *not* result in activation of bone formation. Several other anabolic agents have some clinical potential and are currently in phase II and III trials. For example, growth hormone and insulin-like growth factor-I (IGF-I) are still considered experimental agents, although recombinant human growth hormone (rhGH) has been approved for the treatment of GH deficiency and can increase total body bone density when administered to men and women for more than 1 year [4]. In catabolic states, such as burns, hip fractures, and major surgery, short-term use of IGF-I, GH, and GH-releasing peptides is currently being investigated. Recently, Boonen *et al.* [5] noted that IGF-I/IGFBP-3 (IGF binding protein-3) complex prevented significant femoral bone loss following hip fractures in elderly women.

This chapter examines the central pathways that control bone formation and thereby are likely to be operative during anabolic treatment. Particular focus centers on the IGF regulatory system, since several of these agents, including NaF and PTH, as well as GH, work at least in part by expression of this peptide within the skeleton. With the approval of PTH (1-34), it is probable that PTH (1-84) will enter the market sometime in 2004. PTH-related peptide (PTHrP) also has anabolic properties when administered intermittently on a daily basis. Trials with this peptide sponsored by the National Institutes of Health (NIH) are currently in progress. The future of anabolic agents in treating osteoporosis is promising, especially in light of the very positive clinical experience with hPTH (1-34).

**ANABOLIC AGENTS THAT STIMULATE BONE FORMATION**

Pharmacologic agents undergoing clinical trials but not approved in the U.S. for primary or secondary osteoporosis
- Growth hormone (GH)
- Insulin-like growth factor-I (IGF-I)
- Sodium fluoride
- Bone morphogenetic proteins (BMPs)

Anabolic agents approved in the U.S. for postmenopausal osteoporosis
- PTH (1-34) administered daily for 18 months

Agents with potential utility as anabolic factors in osteoporosis and currently under investigation
- BMPs
- IGF-I/IGFBP-3 (IGF-I complexed to insulin-like growth factor binding protein-3)
- PTH-related peptide (PTHrP)
- IGFBP-5 (insulin-like growth factor binding protein-5)
- Transforming growth factor-beta (TGF-β)
- BMP-2

**FIGURE 17-1.** Anabolic agents that stimulate bone formation.

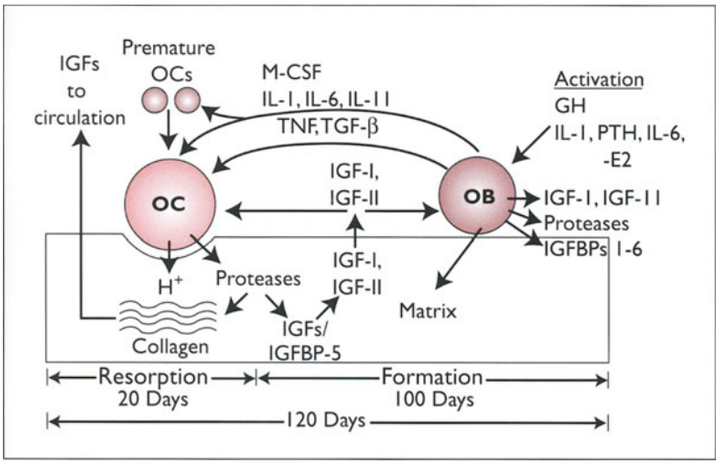



**FIGURE 17-2.** Hormonal regulation of bone remodeling. The bone remodeling unit is a tightly coupled entity. Activation of remodeling occurs with estrogen withdrawal and with administration of growth hormone (GH), thyroxine, parathyroid hormone (PTH), and other cytokines. It is currently thought that the initial regulatory signals exerted by these agents arise from direct interactions with specific receptors in osteoblasts (OB). Release from OB of various cytokines then modulates the maturation, proliferation, and differentiation of osteoclasts (OC), the primary bone-resorbing cell. Among the several cytokines that affect OC, interleukins (ILs) 1, 6, and 11 appear to be particularly important. In response to osteoclastic bone resorption, insulin-like growth factor (IGF) I and II, which have been embedded in the bone matrix complexed to matrix binding proteins, are released and likely participate in the recruitment, proliferation, and activation of new osteoblasts, which replace the resorbed bone (see also Chapter 1)[6]. IGFBP—insulin-like growth factor binding proteins; M-CSF—macrophage colony-stimulating factor; TNF—tumor necrosis factor; TGF—transforming growth factor.

## Insulin-like Growth Factor

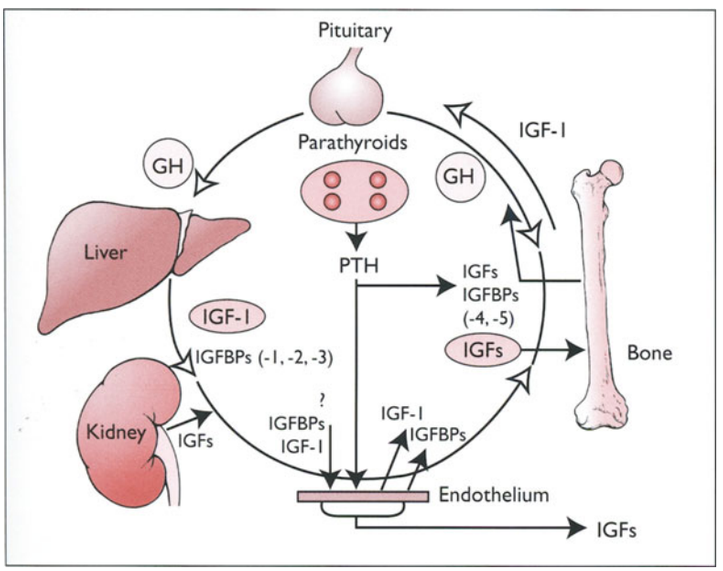



**FIGURE 17-3.** The circulating insulin-like growth factor (IGF) regulatory system. This system is complex and redundant, being composed of the same elements as is the skeletal IGF system. IGF-I is produced by many cells and constantly shuttles in and out of the circulation. Most circulating IGF exists bound to one of several specific binding proteins (BPs). At least six IGFBPs are known to exist and are produced independently by separate genes. The dominant circulating BP is IGFBP3, which depends on growth hormone (GH) for its production. IGF-I, IGF-II, and BP3 also are bound in the circulation to a 70-kd protein called the acid-labile subunit (ALS), giving rise to a stable ternary complex. PTH—parathyroid hormone.

**A. THE IGF REGULATORY SYSTEM IN BONE**

Ligands
- IGF-I, IGF-II

High affinity IGF binding proteins (IGFBPs)
- IGFBPs 1-6*

IGF receptors
- IGF-IR
- Type II IGF receptor

IGFBP proteases
- IGFBP-3 proteases (prostate specific antigen and other serine proteases)
- IGFBP-4 proteases (not identified as yet)
- IGFBP-5 proteases (matrix metalloproteinases)

**The IGFBPs can shuttle IGF to and from tissue sites; however, they can also enhance or antagonize the actions of IGFs at the receptor by competing for binding. IGFBP-4 is a purely inhibitory IGFBP, whereas IGFBP-5 tends to enhance IGF activity while at the same time binding to extracellular matrices including hydroxyapatite. IGFBP-3 is the principal circulating IGFBP; it can enhance or antagonize IGF action.*

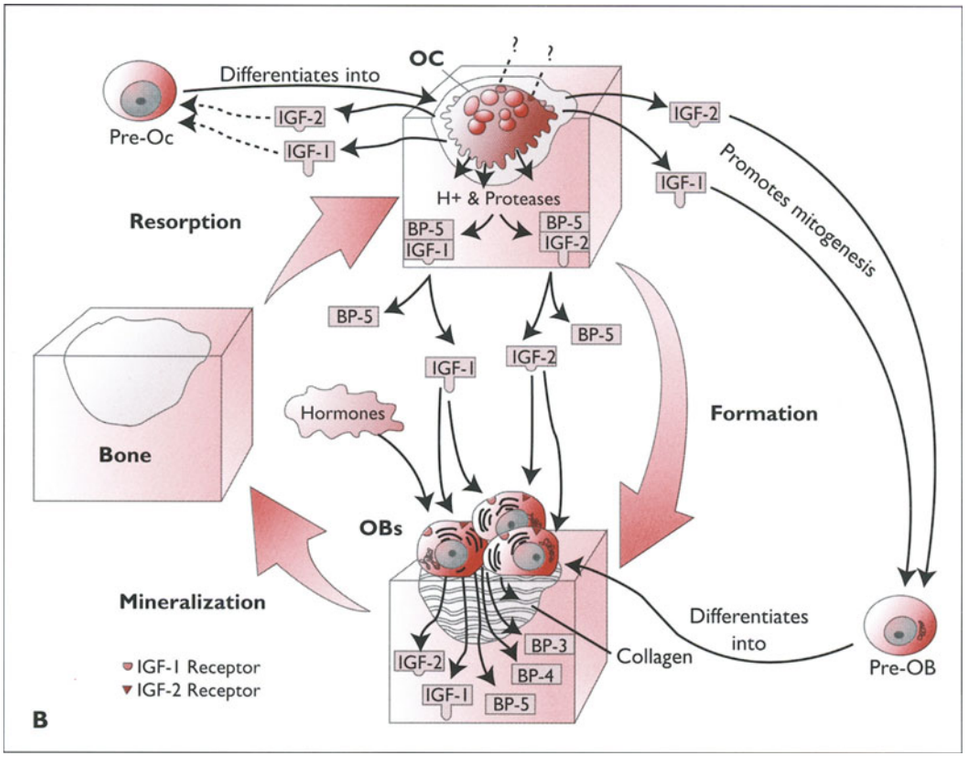



**FIGURE 17-4. A,** Components of the IGF regulatory system in bone. **B,** Osteoblasts (OB) synthesize IGFs. IGF-II is more abundant than IGF-I in the skeleton and in the circulation. Circulating IGF-I concentrations decline with age, and skeletal IGF-I content of cortical and trabecular bone is lower in specimens from elderly persons than from younger individuals. IGFBP-5 anchors IGF to the hydroxyapatite crystal. (Rosen, unpublished data.) BP—binding protein; OC—osteoclasts. (Part B *redrawn from* Yvonne Walston, CMI, ©1997; with permission.)

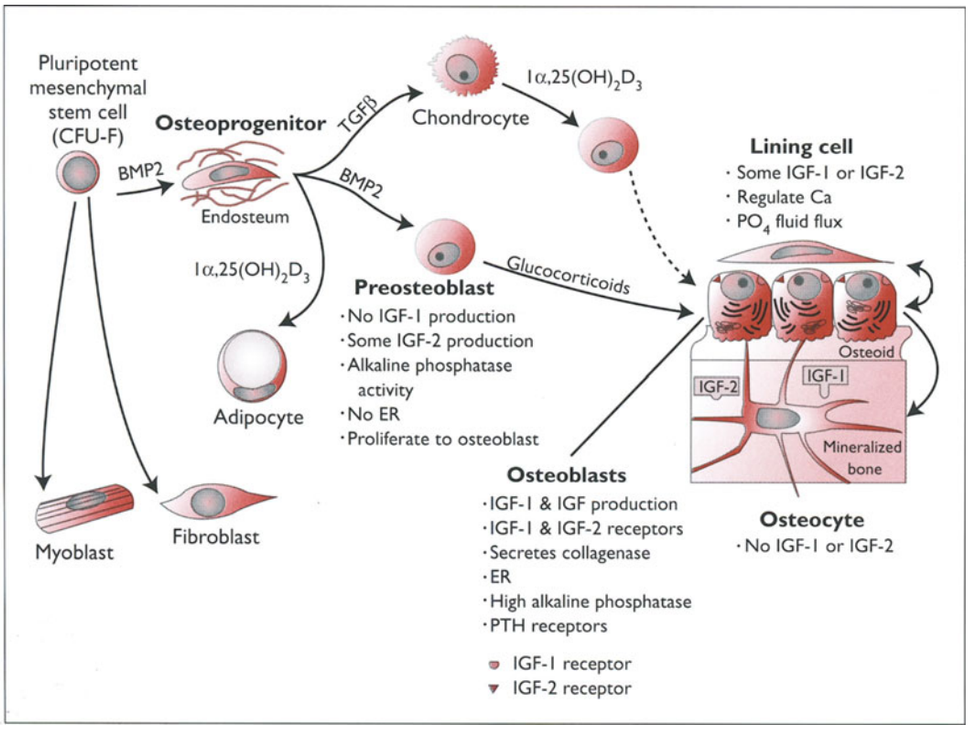



**FIGURE 17-5.** Osteoblast production. The proliferation and differentiation of osteoblasts from pluripotent mesenchymal stem cells (CFU-F) is an elaborate and well-orchestrated process under local and systemic regulation. Recently, cbf1, a protein that serves as a transcription factor for numerous genes, has been shown to be a major switch in the initiation of osteoblast differentiation. IGF-I is also a critical factor later in the differentiation pathway. ER—estrogen receptor; TGF—transforming growth factor; BMP—bone morphogenetic protein. (Rosen, Unpublished results). (*Redrawn from* Yvonne Walston, CMI, ©1997; with permission.)

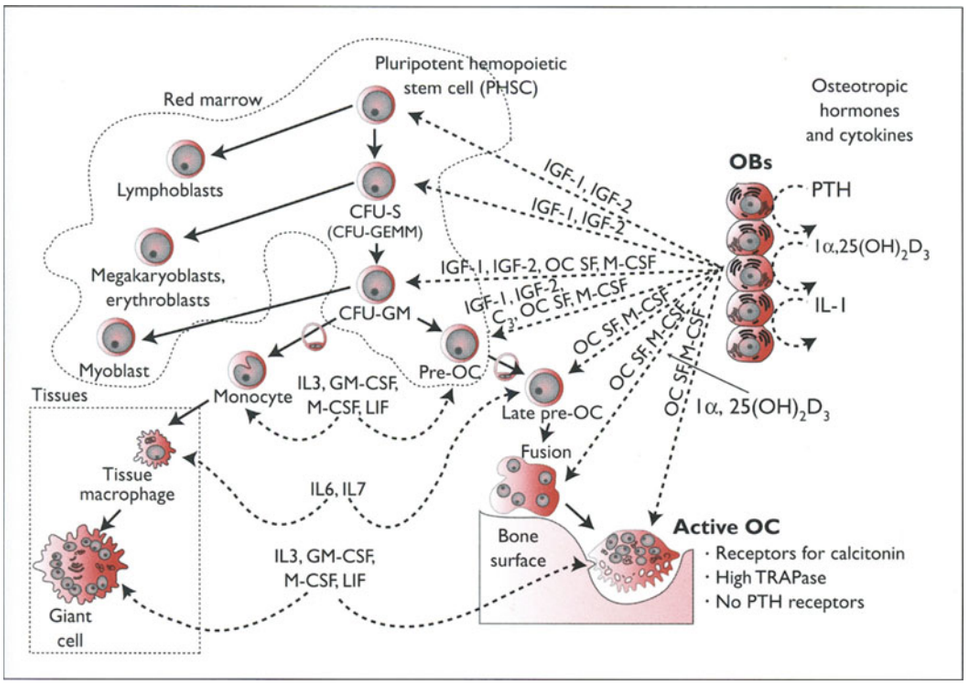



**FIGURE 17-6.** Osteoclast production. Osteoclastogenesis is the process of recruiting pluripotent hematopoietic stem cells (PHSC) into multinucleated giant cells that can secrete protons and proteases. The formation of osteoclasts (OC) is a complex process involving terminal differentiation and fusion. Several cytokines and growth factors, all originating from osteoblasts (OB), orchestrate the process [6]. CFU—colony-forming unit; CFU-S—colony-forming unit stroma; GM—granulocyte monocyte; GM-CSF—granulocyte-monocyte colony-stimulating factor; LIF—leukokinin-inhibiting factor; OC—osteoclast stromal factor; PTH—parathyroid hormone. (*Redrawn from* Yvonne Walston, CMI, ©1997; with permission.)

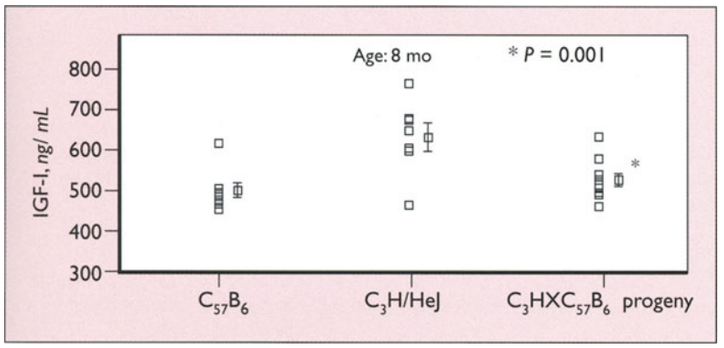



**FIGURE 17-7.** Genetic interaction between insulin-like growth factor (IGF)-I and bone. Although IGF-I is a key factor in bone remodeling, the relationship between circulating IGF-I and bone mass is not understood. Recent studies in mice have proved very illustrative, however. In two inbred strains of healthy mice, there is an approximately 40% difference in bone mineral density (BMD), with C34 mice having greater bone mass than C57B6 animals [7]. Circulating IGF-I concentrations differ by the same degree, with C3H mice exhibiting much higher values throughout life [8]. Mating between these two strains results in a first generation of mice in which IGF-I and BMD are closely correlated, and the serum concentrations are intermediate between high and low IGF-I ($P$ = 0.001). IGF-I production also is higher at the osteoblast level in C3H than B6, and there is greater production in vitro of bone-forming colonies from C3H osteoblasts [8].

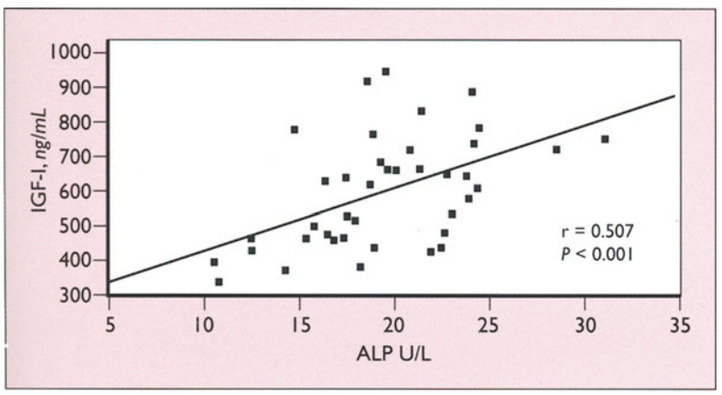
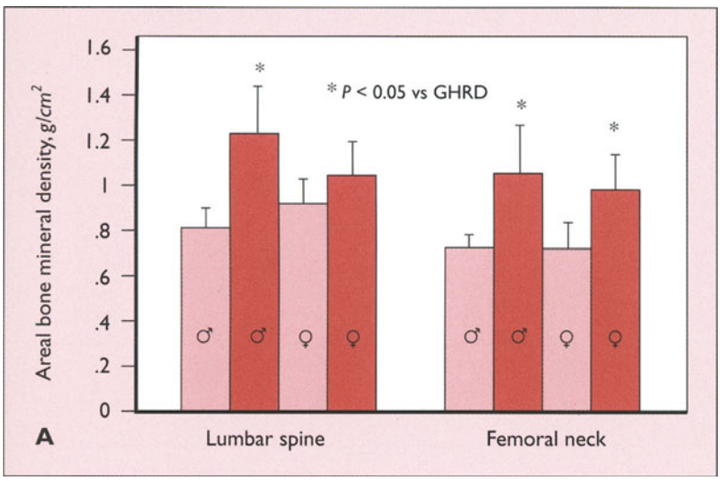



**FIGURE 17-8.** Relationship between circulating insulin-like growth factor (IGF)-I and osteoblast function in 32-week-old mice. There is a highly significant correlation between serum alkaline phosphatase (ALP) activity and serum IGF-I concentration. Circulating IGF-I reflects skeletal IGF-I content as well as the ability of osteoblasts to synthesize and export alkaline phosphatase [9].



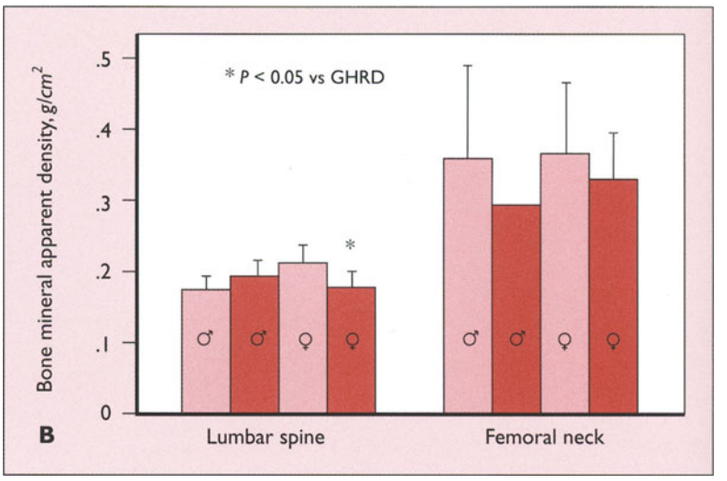
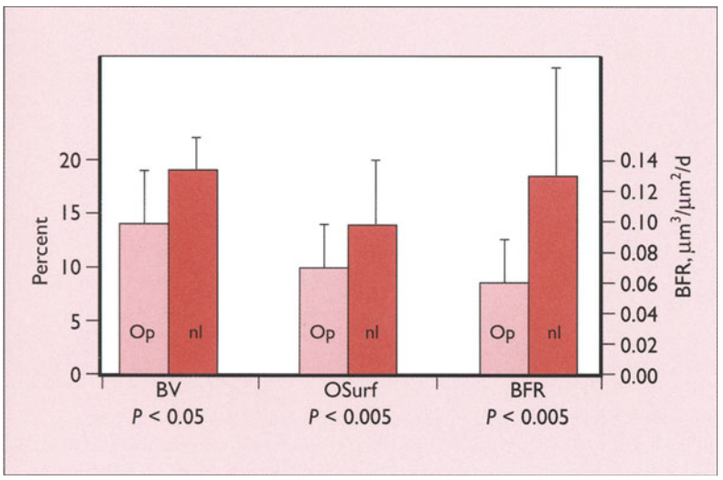




**FIGURE 17-9. A**, Relationship between insulin-like growth factor (IGF) status and bone mass. Growth hormone (GH)-receptor deficiency (GHRD), the syndrome of complete resistance to GH (Laron-type dwarfism), is an autosomal recessive disorder characterized by clinical features of GH deficiency (dwarfism) but normal or elevated GH concentrations. Adults with this condition are extremely short but have normal reproductive, thyroid, and other hormonal status. Circulating IGF-I concentrations in GHRD are extremely low (about 25 ng/mL, compared with normal values of about 250 ng/mL). **B**, Bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DEXA) is significantly lower in men and women with GHRD than in age-matched controls. However, correction of DEXA values for bone size removed this deficit. Thus, differences in bone mass in adults with GHRD are accounted for by differences in the size of bones, not in the mineral content per unit of bone matrix (see also Fig. 1-24 in Chapter 1). Dynamic histomorphometric features of trabecular bone in adults with GHRD are normal. (*Adapted from* Bachrach *et al.* [10].)



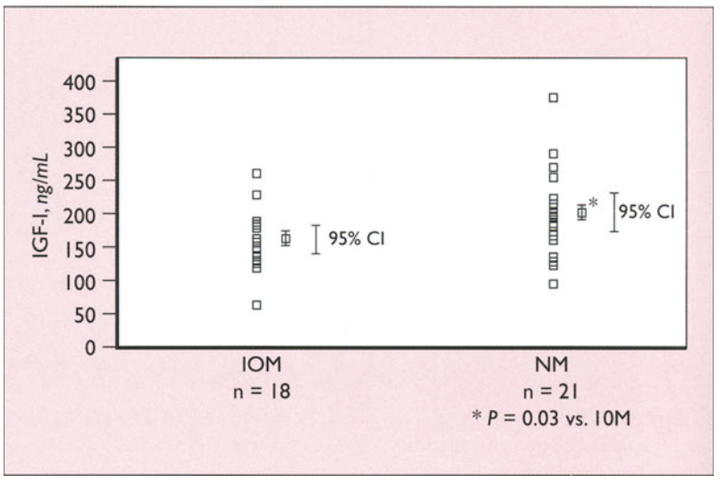




**FIGURE 17-10.** Role of insulin-like growth factor (IGF)-I in idiopathic osteoporosis in males (IOM). Several reports of postmenopausal women have been unable to show a significant correlation between IGF-I concentrations and bone mineral density (BMD) [11,12]. This contrasts with findings in IOM, a condition associated with normal biochemical evidence of bone turnover but reduced bone formation defined on bone biopsy [13]. This graph shows bone volume (BV), an index of trabecular bone mass; osteoid surfaces (OSurf), the fraction (%) of bone surfaces undergoing bone formation activity; and bone formation rate (BFR) expressed in $\mu m^3$ per $\mu m^2$ of bone area per day. Trabecular bone mass and formation characteristics are lower in osteoporotic men than in normal controls. Op—osteoporotic; nl—normal.

**FIGURE 17-11.** Serum insulin-like growth factor (IGF)-I concentrations in men with and without osteoporosis. Although there is considerable overlap, average IGF-I concentrations are lower in osteoporotic men. IOM—idiopathic osteoporosis in males; NM—normal men.

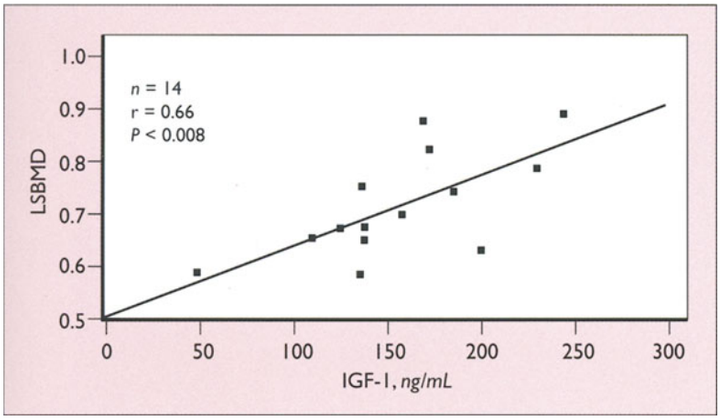



**FIGURE 17-12.** Relationship between circulating insulin-like growth factor (IGF)-1 concentrations and lumbar spine bone mass density (LSBMD) in osteoporotic men. In this series of idiopathic osteoporosis in males (IOM), a highly significant relationship was found between circulating IGF-I and BMD, as opposed to that in normal men and women. It is likely that the designation IOM applies to a group of heterogeneous disorders. IGF-I may not be an important factor for all of them, accounting for the substantial degree of overlap shown in Figure 17-11. However, it appears that diminished IGF-I status contributes to low bone mass for at least some, or even most, affected men. Whether this effect represents a failure of adequate peak bone mass acquisition or of adult bone maintenance is unknown.

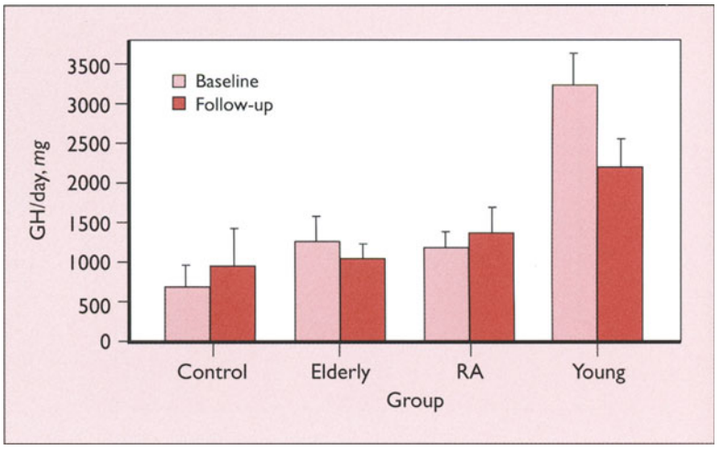



**FIGURE 17-13.** Alterations in the growth hormone (GH)–insulin-like growth factor (IGF)-1 axis in health and disease: the effect of age. Normal human aging is associated with a marked decline in GH secretion, leading to lower circulating levels of IGF-I for each decade after the age of 50 years [14]. This figure shows integrated GH concentrations and an approximation of total daily GH secretion in healthy young and old individuals and in patients with rheumatoid arthritis (RA). GH levels were higher in the young group than the control group ($P = 0.0002$) and the elderly and RA groups ($P = 0.002$). When baseline values were compared with follow-up, there was a significant decrease in the young group compared to the control and RA groups ($P = 0.01$). (*Adapted from* Roubenoff *et al.* [15].)

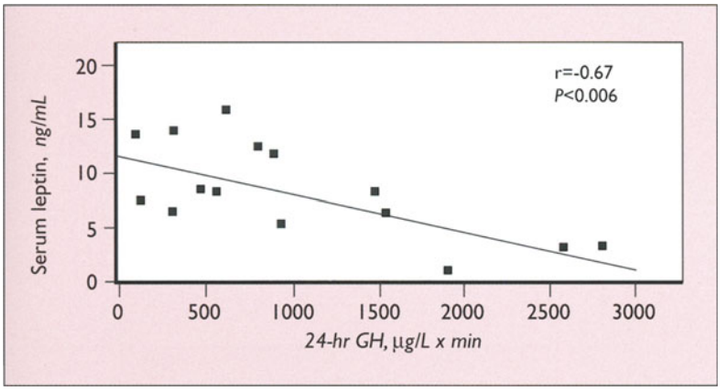



**FIGURE 17-14.** The effect of obesity on growth hormone (GH) status. Obesity has long been known to be associated with diminished GH secretion. Recent evidence suggests that this phenomenon may be the result of an inhibitory effect of leptin, a peptide hormone produced by fat cells [15]. This figure shows a strong negative relationship between circulating leptin and 24-hour integrated GH concentrations.

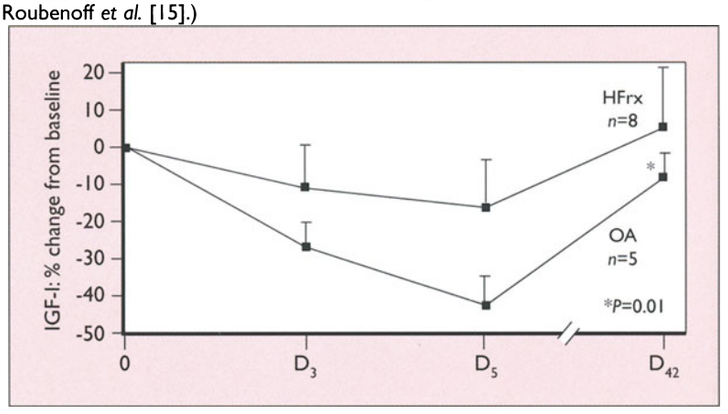
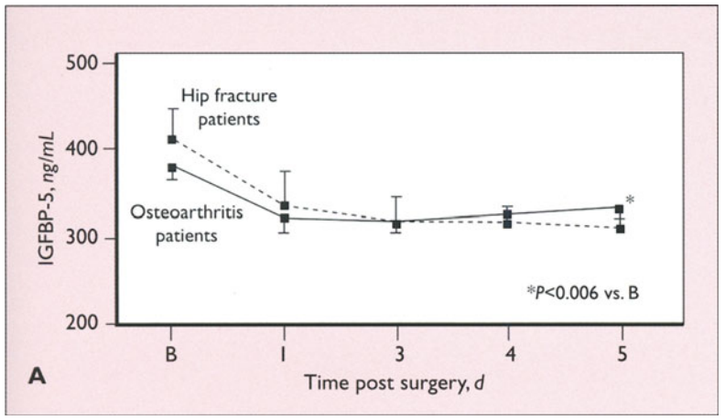
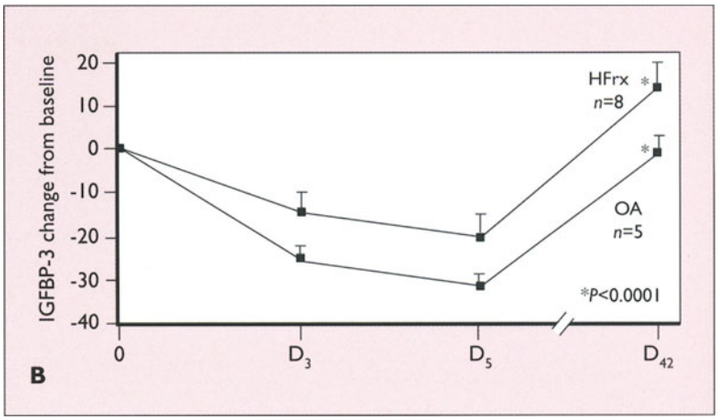



**FIGURE 17-15.** Effect of catabolic illness on insulin-like growth factor (IGF)-1 status. IGF-I production is critically dependent on nutritional state and whole body protein status. In patients with hip fractures, IGF-I concentrations drop within 24 hours of injury and decline further after surgical fixation. This figure shows two groups of patients undergoing surgery for hip fracture or for prosthetic joint replacement for osteoarthritis. $D_3$, $D_5$, $D_{42}$—days 3, 5, and 42 after fracture; Hfrx—hip fracture; OA—osteoarthritis.



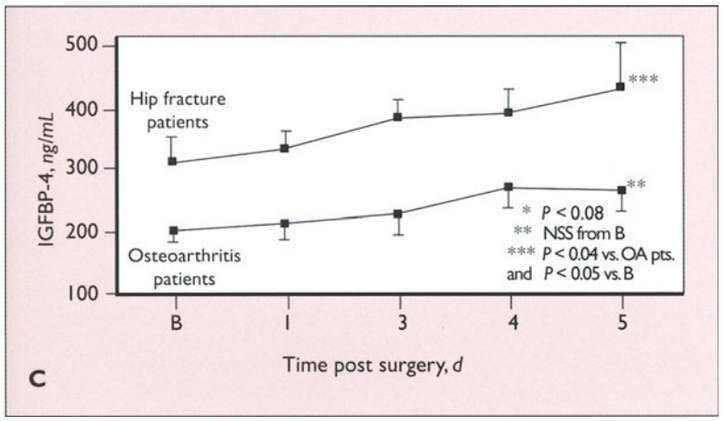




**FIGURE 17-16.** Effect of surgical stress on insulin-like growth factor (IGF)-1 binding proteins. As explained earlier, circulating IGF-1 is bound largely to several binding proteins (BPs). Some of these BPs enhance IGF action on bone, whereas others are inhibitory. Thus, understanding changes in overall IGF-1 status is complicated by simultaneous alterations in BP concentrations. This figure shows coordinate changes in IGFBPs 3, 4, and 5 following hip surgery. BPs 3 and 5 drop precipitously, whereas BP4, an inhibitory BP that blocks IGF-1 action, actually increases. **A,** Changes in IGFBP-5. **B,** Changes in IGFBP-3. **C,** Changes in IGFBP-4. Hfrx—hip fracture; OA—osteoarthritis. (Rosen, Unpublished data).

# Human Growth Hormone

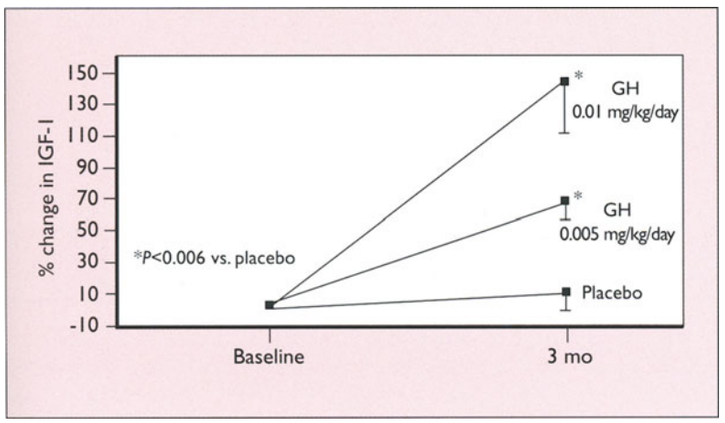



**FIGURE 17-17.** Effect of recombinant human growth hormone (rhGH) on bone turnover and bone mineral density (BMD) in older individuals. Given the fact of age-related declines in GH and IGF-1 status as well as the loss of BMD with age, it seemed possible that replacement of GH might restore BMD in older men and women. This figure shows that treatment of frail older men and women with rhGH for 1 year led to marked increases in IGF-1 concentration and, in a dose-dependent manner, also stimulated markers of bone resorption.

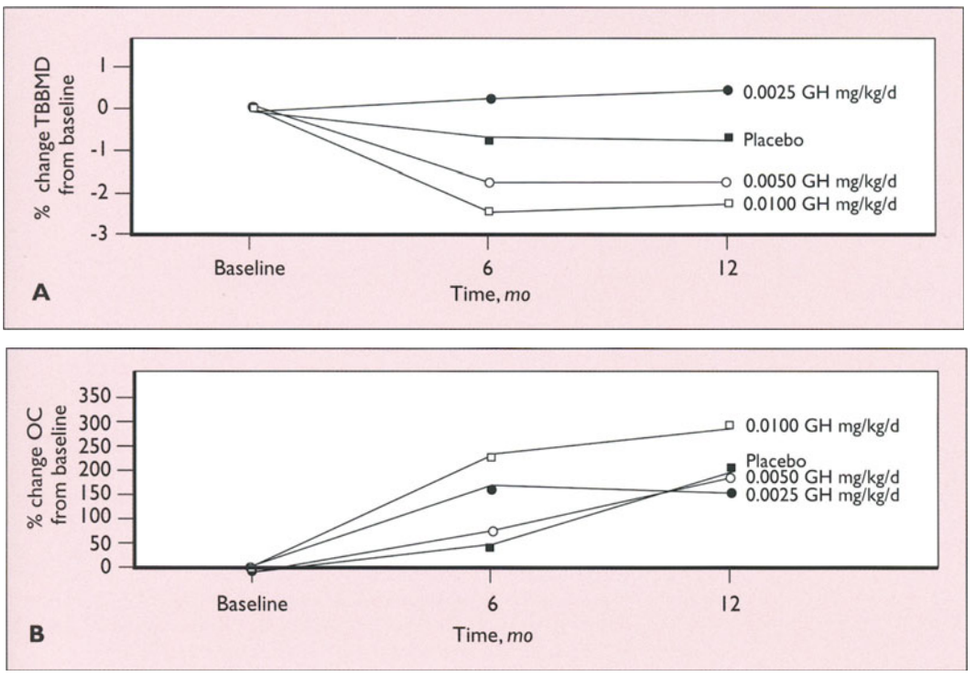



**FIGURE 17-18.** Effect of recombinant human growth hormone (GH) on bone turnover and bone mineral density (BMD) in older individuals. In the same trial described in Figure 17-17, GH stimulated osteocalcin (OC) (**A**), a biochemical marker of bone formation, but had no beneficial effect on total body bone mineral density (TBBMD) (**B**). (*Adapted from* Maclean *et al.* [16].)

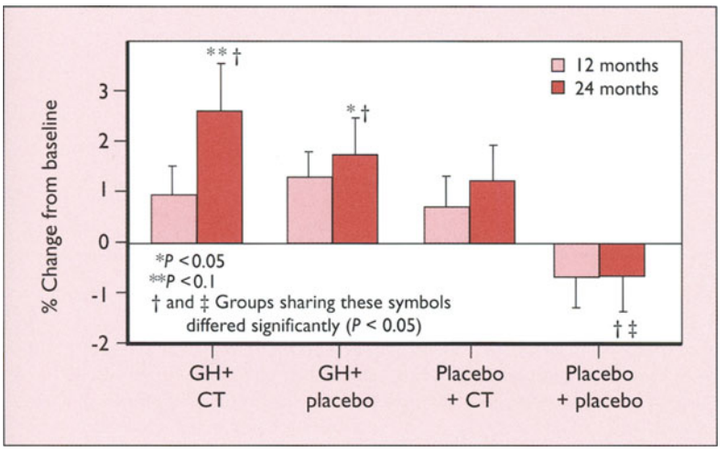



**FIGURE 17-19.** Effect of cyclic growth hormone (GH) with or without calcitonin on bone mineral density (BMD) in osteopenic older women. GH administration increases both resorption and formation marker activity; thus, it is likely that GH promotes an increase in new bone remodeling units, with a concomitant increase in the remodeling space. The hypothesis was tested that administration of recombinant human GH (rhGH) together with the antiresorptive hormone, salmon calcitonin, might permit a greater rise in BMD than would rhGH alone. This figure illustrates the effect on lumbar spine BMD of a 2-year program of GH with or without calcitonin (CT) given every 2 months for 24 months. rhGH stimulated modest increases in BMD, but these were not magnified by CT. The achieved rise in BMD resembles those observed with approved antiresorptive medications. Thus, it appears there is little, if any, therapeutic role for GH in treatment of osteoporosis. (*Adapted from* Holloway *et al.* [17].)

# Parathyroid Hormone

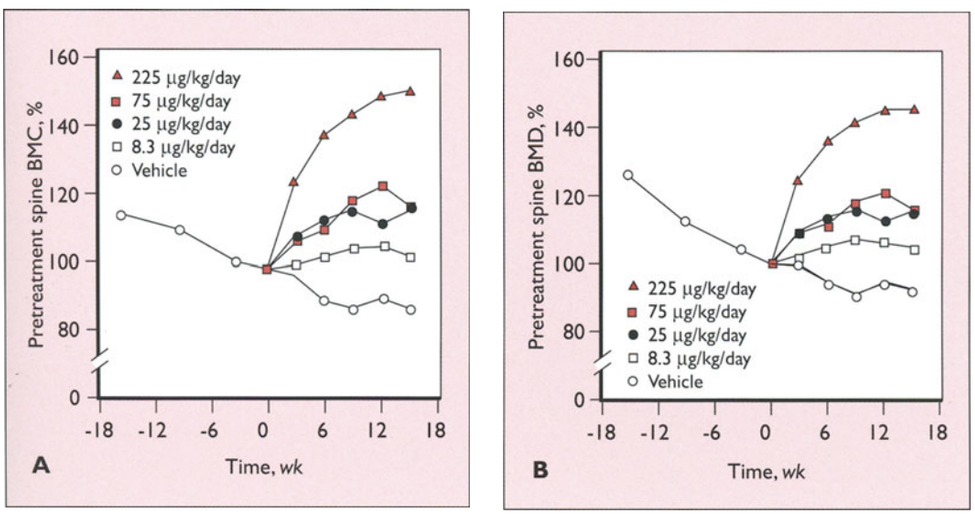



**FIGURE 17-20.** Skeletal effects of exogenous parathyroid hormone (PTH). Although continuously high concentrations of PTH have been associated with bone disease in patients suffering severe primary hyperparathyroidism, intermittent elevation of PTH appears to increase bone mass, particularly in the spine. This figure shows the effects of daily PTH treatment on spine bone mineral content (BMC) and bone mineral density (BMD) in ovariectomized rats. A dose-dependent response is observed [3,18].

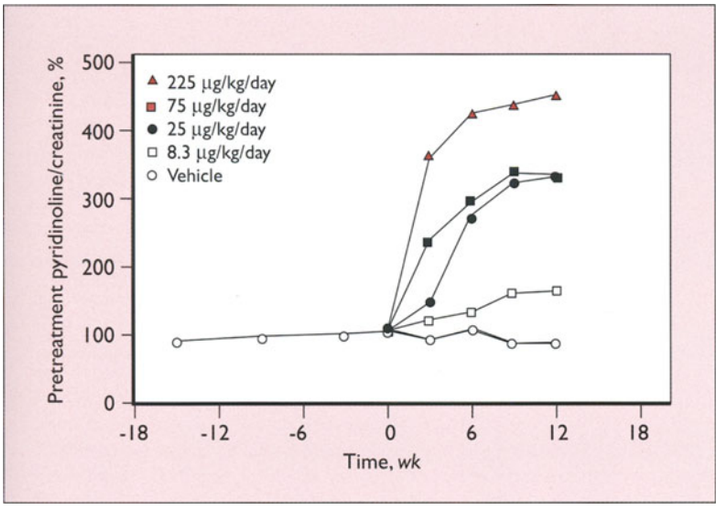
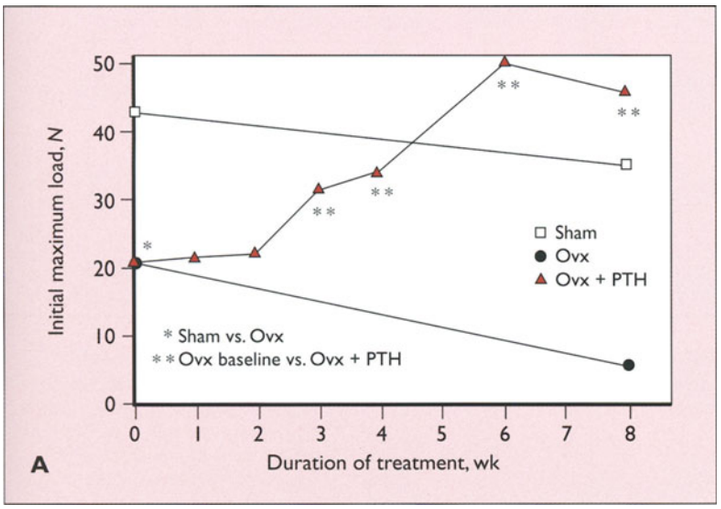



**FIGURE 17-21.** Effect of parathyroid hormone (PTH) on bone turnover in ovariectomized rats. In the same study illustrated in Figure 17-20, PTH led to a dose-related increase in bone turnover indicated by the pyridinoline:creatinine ratio, a resorption marker [3].



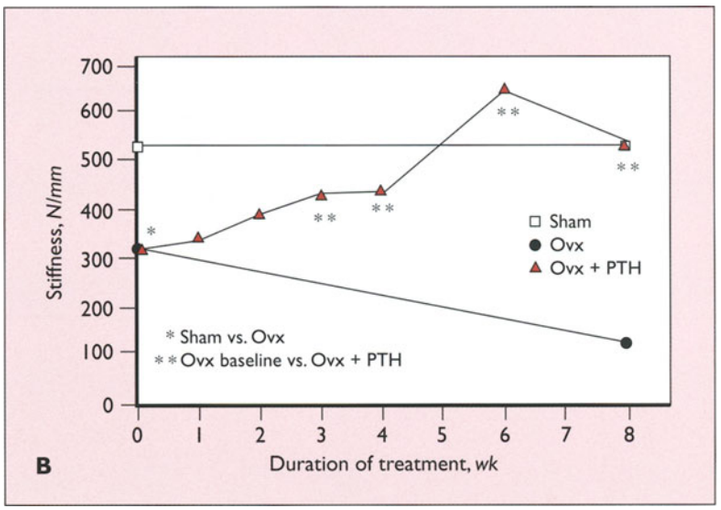




**FIGURE 17-22.** Effect of intermittent administration of parathyroid hormone (PTH) on mechanical competence of bone. In this study, rats were sham-operated on, were ovariectomized (OVX), or had OVX plus treatment with a rat PTH analogue, PTH(1-34). Sham-operated animals had no significant change in maximal load capacity (**A**) or stiffness (**B**), two measures of bone strength. OVX animals were significantly lower in both measures by the time PTH(1-34) injections began, and PTH(1-34) restored these to sham values in several weeks. These changes were associated with improvement in cancellous bone volume and trabecular thickness [3,19].

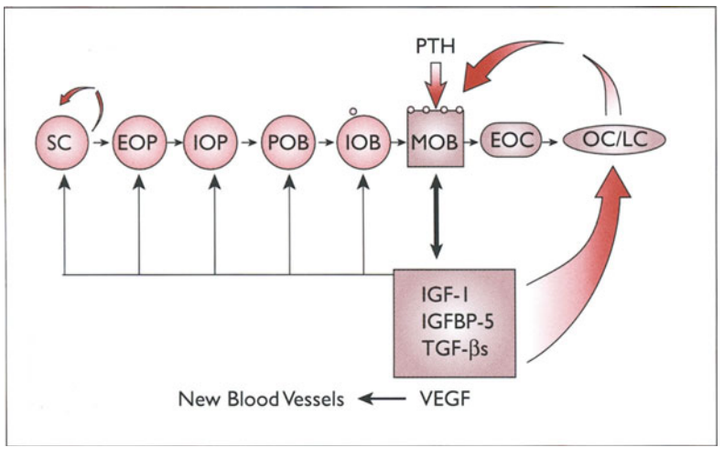
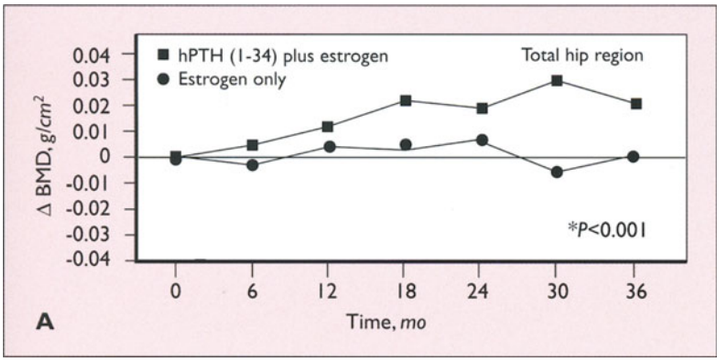
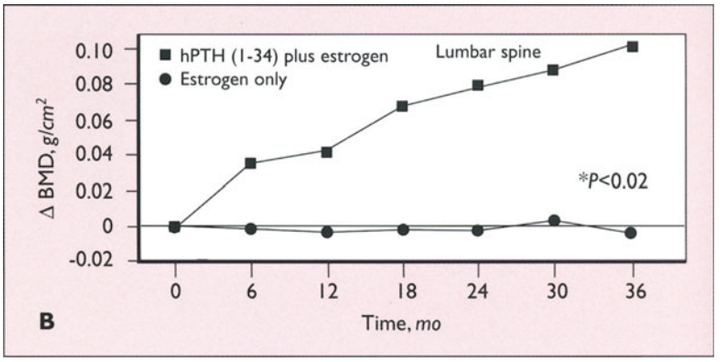



**FIGURE 17-23.** Anabolic actions of parathyroid hormone (PTH) on bone. One mechanism of action by which PTH affects bone is thought to be through the insulin-like growth factor (IGF) regulatory system, with direct induction of IGF-I and several IGF binding proteins (IGFBPs) in osteoblasts [20].



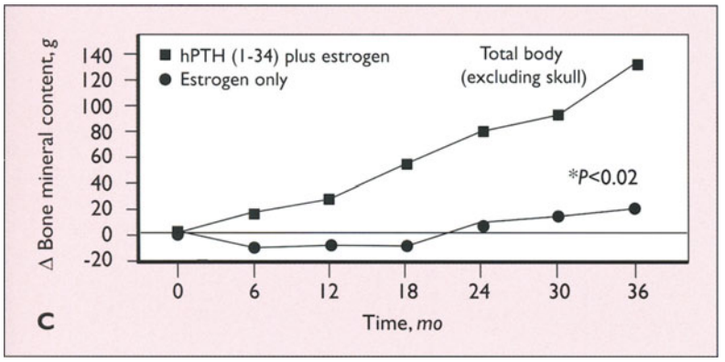




**FIGURE 17-24.** Effects of parathyroid hormone (PTH) (1-34) on bone mineral density (BMD) of postmenopausal women. **A**–**C**, In this randomized trial, human PTH (hPTH) increased bone mass in postmenopausal women who had been receiving hormone replacement therapy for at least 1 year [21]. Results were particularly dramatic at the lumbar spine (**B**). Although PTH(1-34) alone might predictably decrease cortical BMD, the rise in total body bone mineral content in these estrogen-replete women was reassuring (**C**). PTH and its analogues are currently in phase II and III clinical trials for treatment of osteoporosis.

## Sodium Fluoride

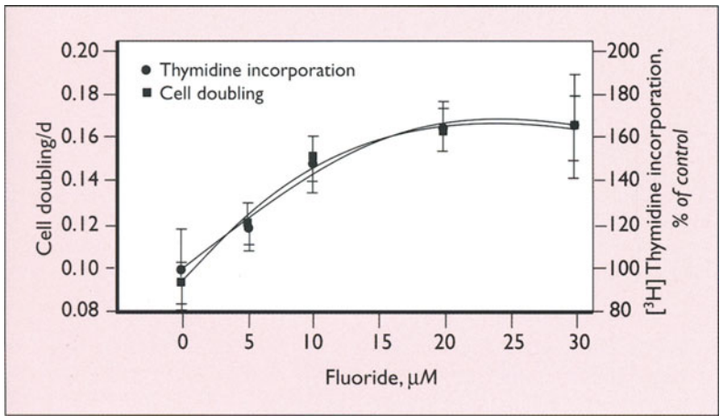



**FIGURE 17-25.** Mitogenic effects of sodium fluoride on bone cells. NaF increases $^{3}$H-thymidine incorporation and promotes cell doubling in a dose-dependent manner. (D. J. Baylink, MD, Loma Linda, CA, Personal communication.)

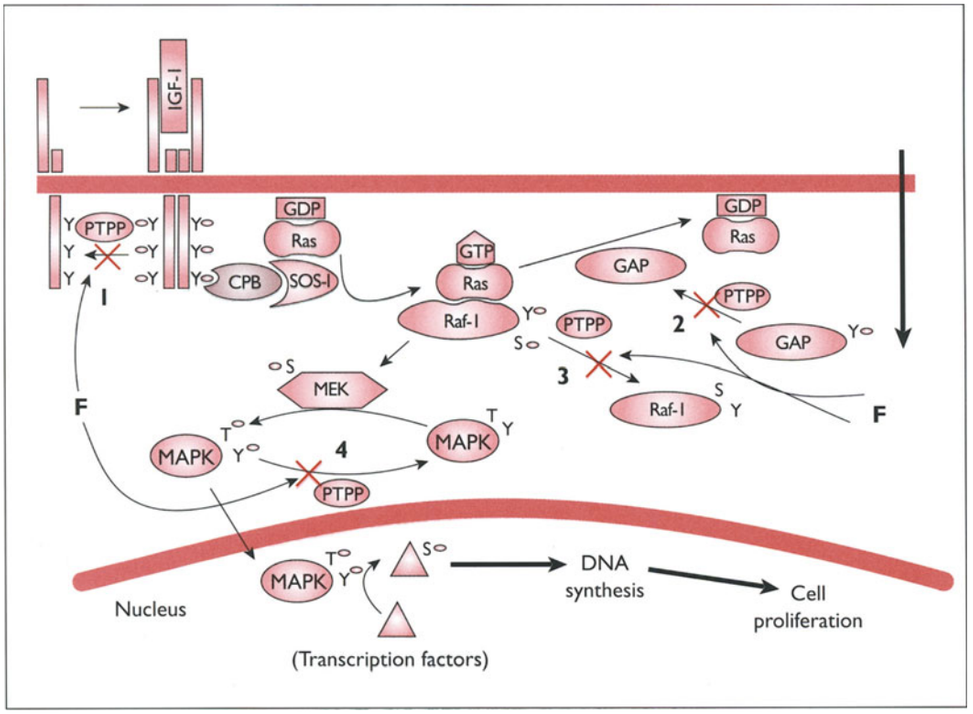



**FIGURE 17-26.** Skeletal actions of sodium fluoride (NaF). The anabolic effects of NaF are related to alterations in several pathways and second messengers for osteoblasts. In particular, it is thought that fluoride inhibits the action of several tyrosine phosphatases, thereby enhancing the actions of MAP kinases. This may lead to greater signaling amplitude through the IGF-I/IRS-1 pathway [22].

**FRACTURE STUDIES USING FLUORIDE: RANDOMIZED DOUBLE-BLIND PLACEBO TRIALS**

| Study | Reduction in Vertebral Fractures | Fluoride dose |
|---|---|---|
| Riggs, 1990 | No | High dose—NIH |
| Kleerekoper, 1991 | No | High dose—NIH |
| Pak, 1994, 1995 | Yes | With moderate doses—mild low BMD |
| Riggs, 1994 | Yes | Moderate dose |
| Ringe, 1998 | Yes | Males with IOM |
| FAVOS, 1998 | No | High dose |

**FIGURE 17-27.** Summary of the trials of sodium fluoride for both sustained-release and monosodium fluoride in relation to vertebral fracture reduction efficacy [1,23,24]. The regulatory status of fluoride salts in the United States is currently unsettled. Controversy remains concerning the quality of fluoride-treated bone and whether claims of antifracture benefit are reliable.

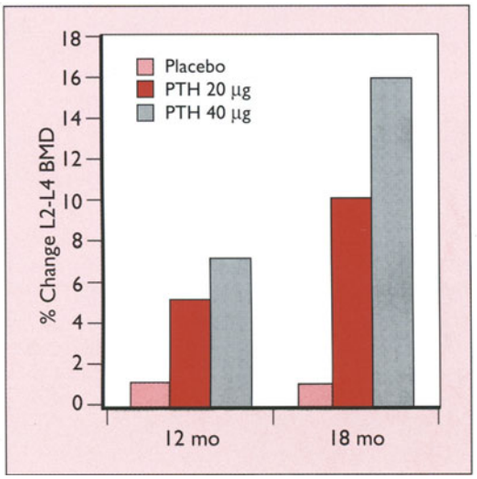



**FIGURE 17-28.** Parathyroid hormone (PTH) (1-34) at doses of 20 and 40 µg per day for 20 months increased spine bone mineral density and reduced fracture risk by more than 50% in postmenopausal women with low bone mass and previous fractures. There were few side effects noted with intermittent PTH therapy in this the largest randomized trial with PTH. Similar results have been obtained in osteoporotic men treated in the same way. In these studies, the form of parathyroid hormone used was the 1-34 N-terminal amino acid fragment of the native hormone. The actions of this fragment, named teriparatide (Forteo; Lilly, Indianapolis, IN), mimic the effects of the intact parathyroid hormone in most ways. Separate human trials of the effectiveness of the intact hormone are under way. (*Adapted from* Neer *et al.* [2]; with permission.)

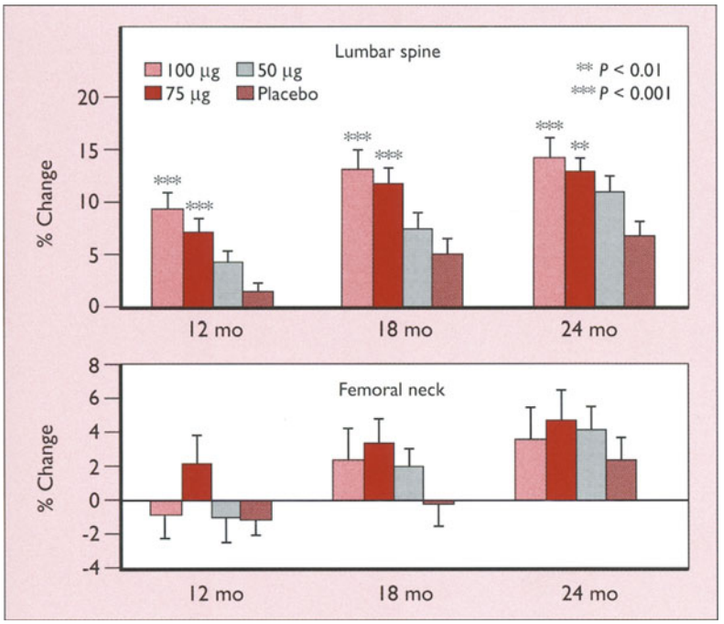



**FIGURE 17-29.** The sequential administration of PTH (1-84), for 1 year, followed by alendronate 10 mg per day for 1 year, was associated with a nearly 15% increase in spine bone mineral density. (*Adapted from* Rittmaster *et al.* [25]; with permission.)

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Page numbers followed by *f* indicate figures.

# C

# D



# E



# F



# G

# M



# N



# O

# P



# Q



# R



# S

## X



## Z

# Color Plates

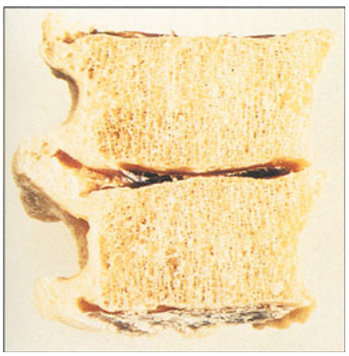
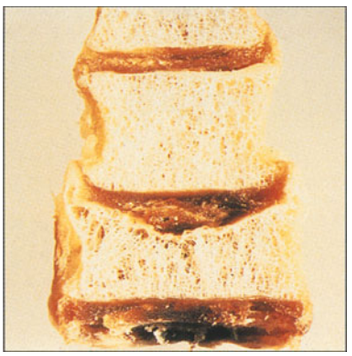


**FIGURE 1-3.** Page 2



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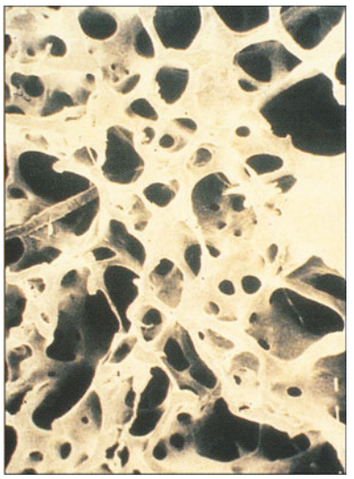


**FIGURE 1-5A.** Page 3

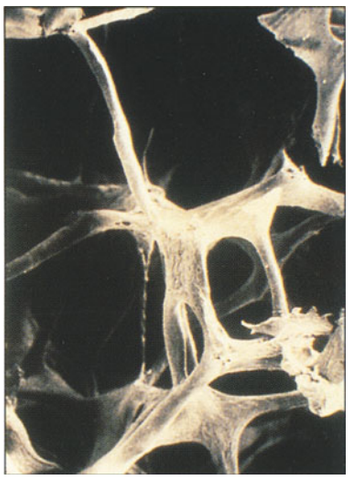


**FIGURE 1-5B.** Page 3

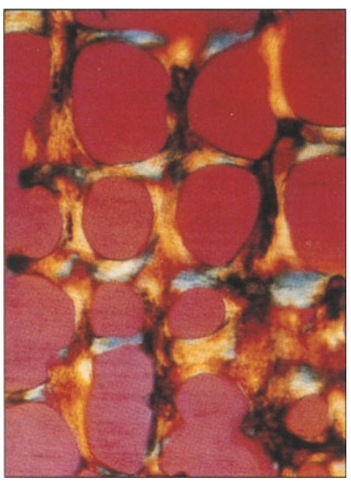


**FIGURE 1-15A.** Page 6

**FIGURE 1-15B.** Page 6

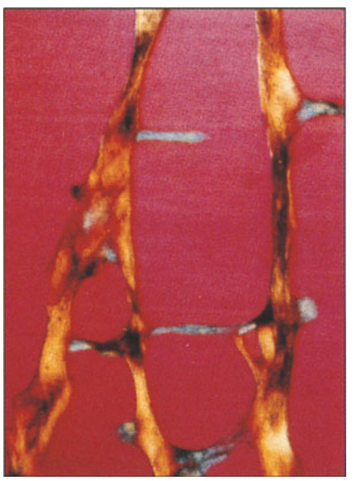


**FIGURE 1-15C.** Page 6

**FIGURE 1-15D.** Page 6

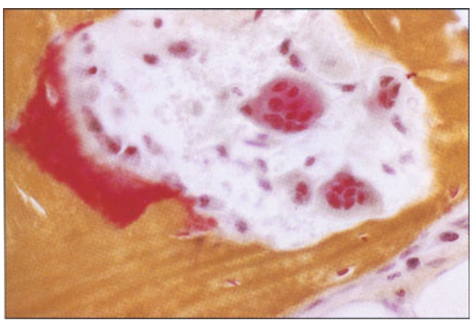


**FIGURE 1-21.** Page 8

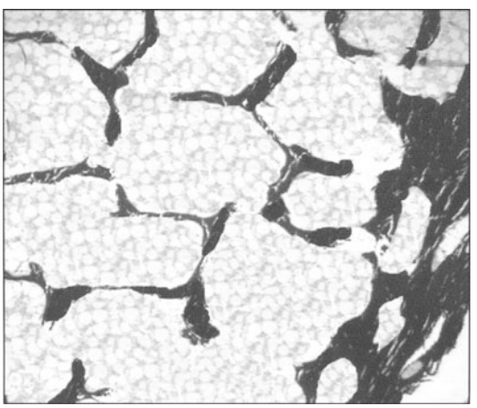


**FIGURE 11-6A.** Page 122

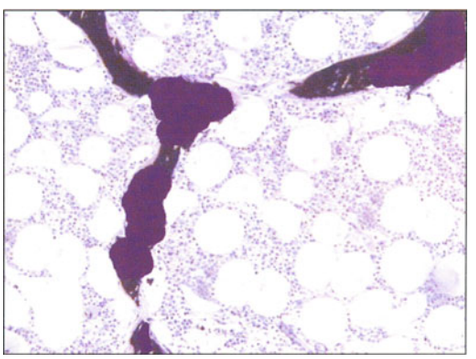


**FIGURE 11-6B.** Page 122

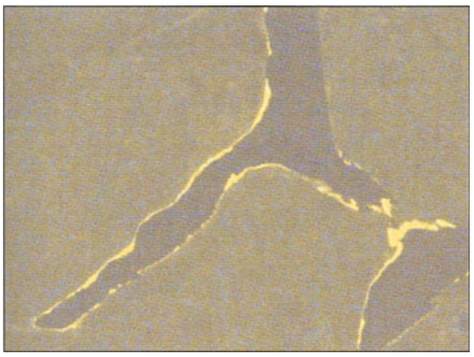


**FIGURE 11-6C.** Page 122

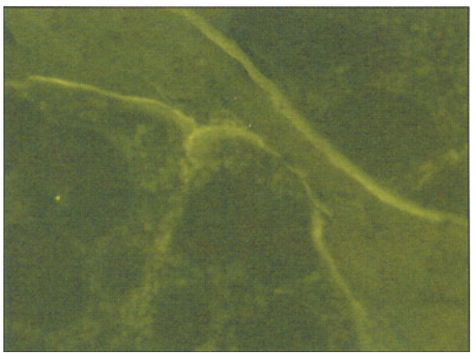


**FIGURE 11-6D.** Page 122

**FIGURE 11-6E.** Page 122

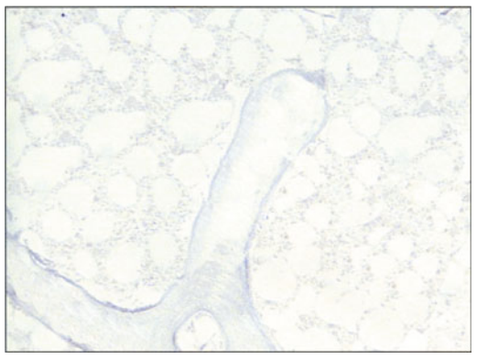


**FIGURE 11-6F.** Page 122

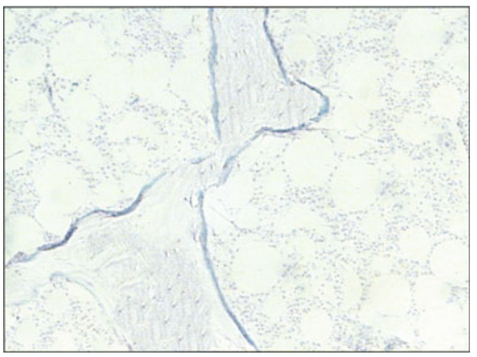


**FIGURE 11-6G.** Page 122

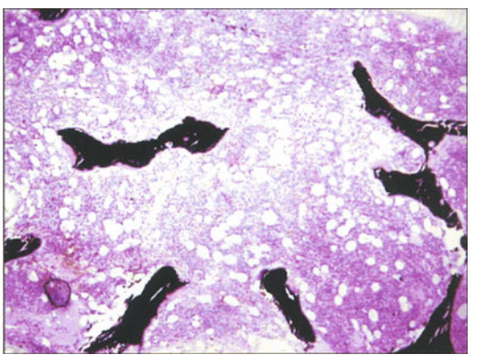


**FIGURE 11-7A.** Page 123

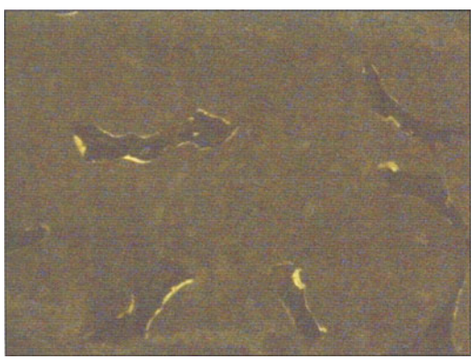


**FIGURE 11-7B.** Page 123

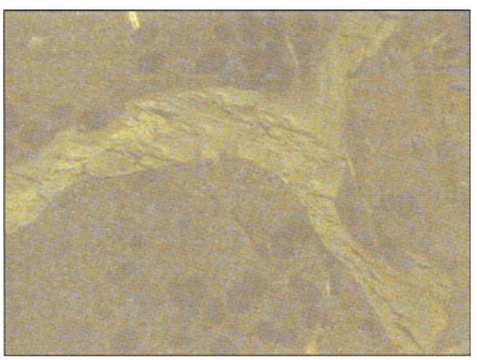


**FIGURE 11-7C.** Page 123

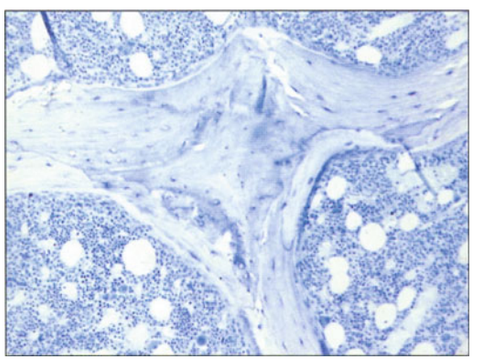


**FIGURE 11-7D.** Page 123

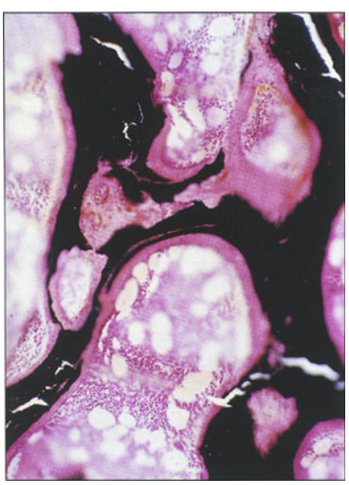


**FIGURE 11-9A.** Page 124

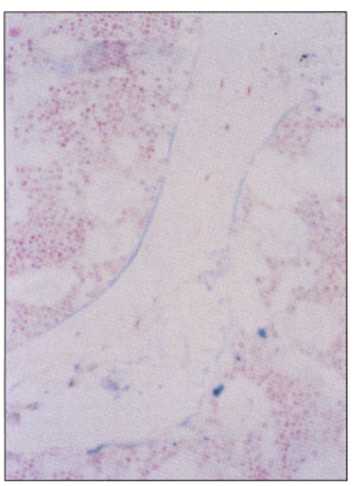


**FIGURE 11-9B.** Page 124

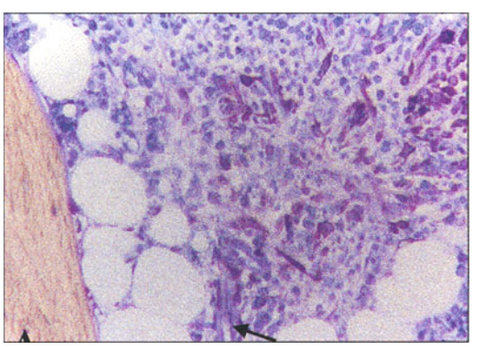


**FIGURE 11-15A.** Page 126

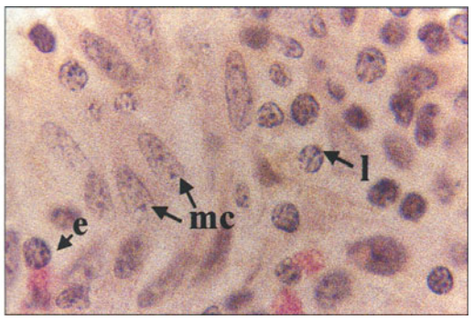



**FIGURE 11-15B.** Page 126

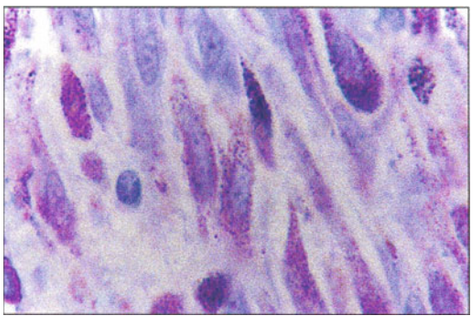


**FIGURE 11-15C.** Page 127

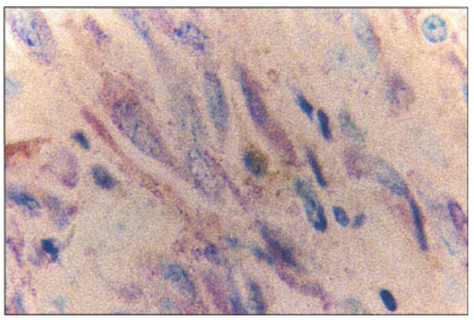
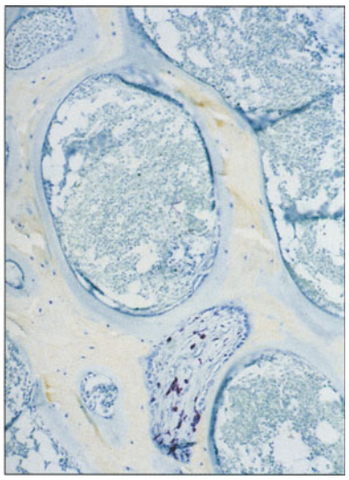


**FIGURE 11-15D.** Page 127



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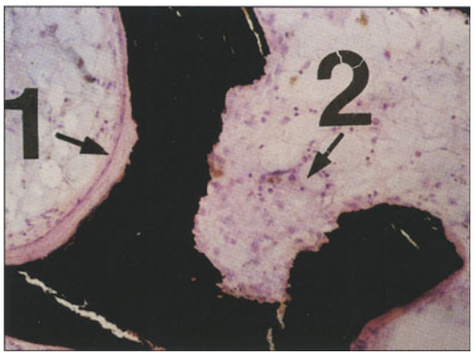


**FIGURE 11-20B.**
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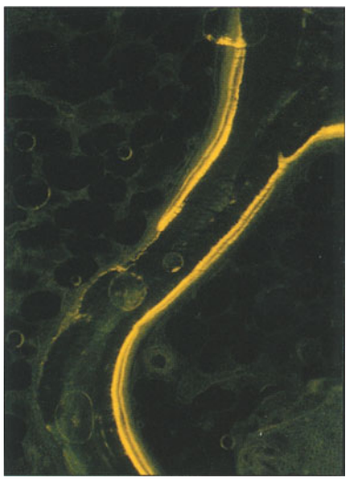


**FIGURE 11-20C.** Page 129

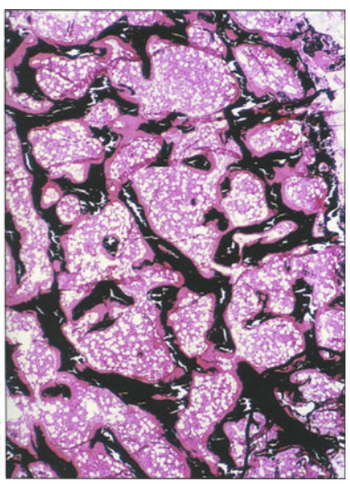


**FIGURE 11-28.** Page 132

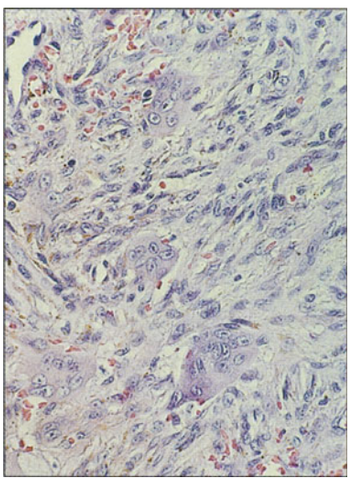


**FIGURE 11-31A.** Page 134

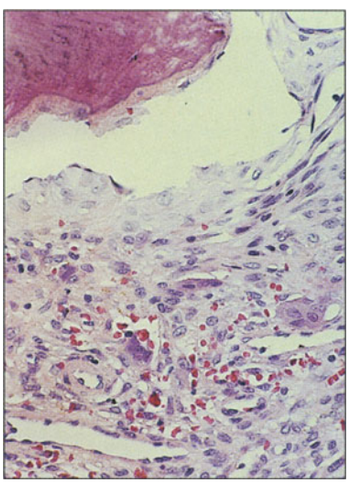


**FIGURE 11-31B.** Page 134

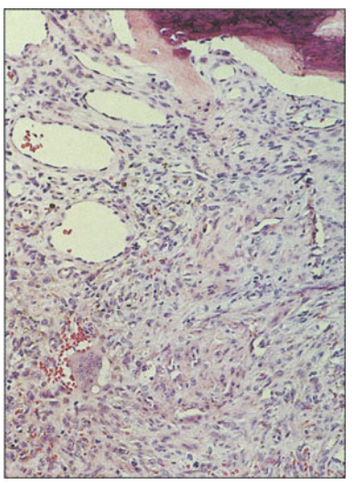
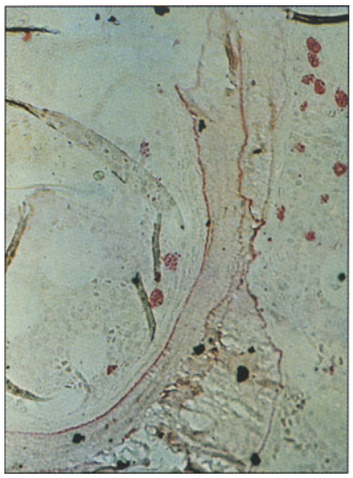


**FIGURE 11-31C.** Page 134



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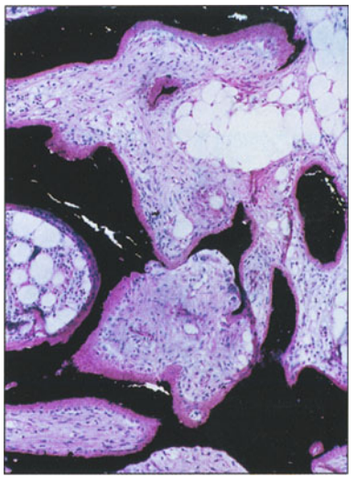

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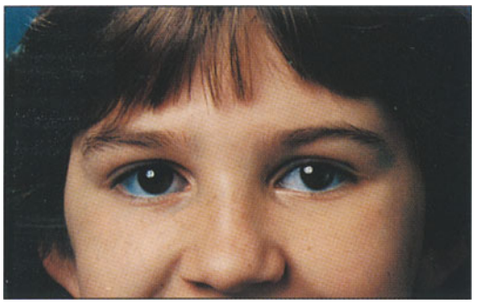

**FIGURE 11-33.**
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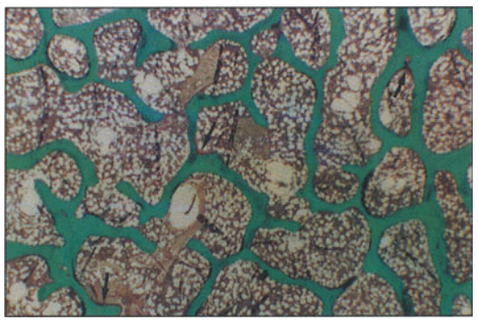

**FIGURE 12-4A.** Page 139

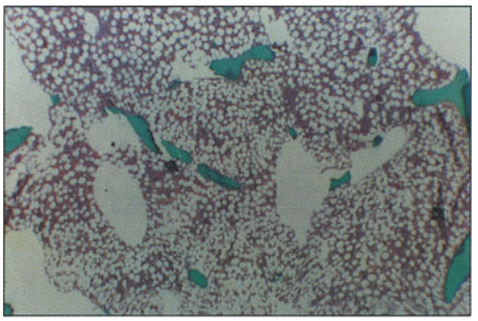

**FIGURE 12-4B.** Page 139

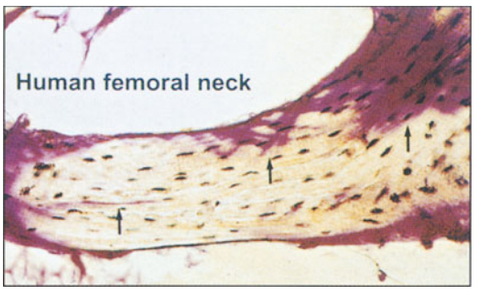


**FIGURE 14-8A.** Page 169